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PATHOLOGY OF TUMOURS

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FORMERLY PATHOLOGIST TO THE ALTRED HOSPITAL CONSLITANT PATHOLOGIST TO THE AUSTIV HOSPITAL FOR CHRONIC DISEASES AND LECTURER ON THE PATHOLOGY OF TUMOURS IN THE UNITERSITY OF MELBOURNE AUSTRALIA

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To mv wife Margaret

PREFACE

This BOOK is the outcome of my special interest in tumours during 20 years as a hospital pathologist. Most of the material on which it is based was studied in the pathology laboratories of the Alfred Hospital Melbourne between the years 1930 and 1945 and some of the work was written in this period during part of which I held also a research appointment in the Pathology Department of the University of Melbourne In a great measure, then the book is a Melbourne product Yet I am fortunate in my present post at the Royal College of Surgeons in that this is in part a research appointment so that during the past two years in addition to carrying out routine duties in the restoration of the museum and in teaching I have also been able to complete the present work. A few comments regarding the contents are necessary

General scope of the nork - While aiming to give a useful general outline of each topic. I also wished the book to be a personal record of my own observations and conclusions. Throughout therefore I have used my own material as fully as possible and have introduced many brief reports of personally studied cases illustrative of the subjects under discussion. For the same reason I have made frequent reference to my own published papers and to my earlier book, ' The Sprend of Tumours in the Human Body the contents of which in many ways supplements that of the present larger work On controversial matters too while indicating that they are controversial. I have preferred to avoid non-committal vagueness and to state plainly my own present opinions even though these may have to be modified in the light of future experience

The book is addressed primarily to pathologists research workers and senior students but I am not without how that clinicians also may find it useful and that even elementary students may find it intelligible. My conviction that much has yet to be learnt from the comparative pathology of tumours is shown by a chapter on this subject in Part I and by sections devoted to it in the chapters of Part II

Illustrations - The figures are all from personally studied material and most of them have not previously been published. With few exceptions they are illustrations of gross type specimens are unnecessary for microphotographs those to whom the book is addressed and indeed are often not very instructive even for elementary students who will learn much more from actual specimens at operations and necropsies and in the museum. In selecting the figures. I have often omitted those illustrating the well known appearances of common tumours such as are to be found in nearly every text book. I have preferred rather to show less familiar and special features and particularly the range of structu e possible in tumours of the less common kinds. I have tried also to avoid needl reduplication of figures showing similar structural types of growth e.g. since the range of structure of squamous cell carcinoma is adequately illustrated for tumours of the skin and oral cavity I have given few or no illustrations of this type of growth in the oesophingus uterus vulva and penis. Most of the figures

References -The reference lists given at the ends of the chapters are far from

are from cases reported in the text, and the legends often supplement the text

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Except where the legends state that special stains were used the figures were prepared from paraffin sections stained by one or another of the ordinary haematoxylin methods The magnification of all figures is given

complete, I know that I have omitted many important references which might have been preferable to some of those included. To the writers of important papers which are omitted, I tender my apologies My excuse is that no man car possibly read more than a small fraction of the literature on even a small section of the subject, and I have preferred to base my discussion on what I have read or at least consulted. For a writer to give long lists of references to papers he has not seen is always futile and often dishonest. On controversial matters. I have tried to select my reading impartially, but I am well aware that I may not always have succeeded in this Whatever omissions I may be guilty of in my reference lists. I can at least claim that they comprise works which with very few exceptions I have personally consulted in the original. Works listed in bold type are those which I have found particularly useful as marking important discoveries or as

good reviews with useful lists of further references, or for other reasons which I have in many instances stated in parentheses Acknowledgments - My happy association during 15 years with the members of the medical and surgical staff of the Alfred Hospital-too many to mention all by name-placed me deeply in their debt for stimulating discussions in ward and laboratory and for free access to the records of their cases Individual acknowledgment is made in the text to those who have permitted me to record the histories of privately treated patients. With pleasure I express also my indebtedness to Professor P MacCallum, of the University of Melbourne, with whose Department I was happily associated as a research worker for nearly 18 years Many others of my fellow pathologists, both in Australia and Great Britain.

indebtedness to two of them. Most of my manuscript was read by Professor G W Nicholson formerly of Guy's Hospital who made many valuable suggestions and criticisms. Those who value his writings as highly as I do will understand how privileged I feel to have had such a mentor My second special debt is to Dr Leila M Hawksley, formerly pathologist to the Cancer Hospital London who has given me many valuable specimens of unusual tumours. especially of the gonads, bones and muscles, and who has helped me to clarify my ideas on many debatable points

have helped me by the exchange of specimens and ideas, I can thank them only collectively for they are too numerous to name. But I must record my special

The dedication of this book to my wife Margaret Willis is more than usually appropriate, for not only has she given unstinted wifely encouragement to studies which meant surrender of many of our accustomed pleasures but she also made many of the microscopical preparations aided in many dissections and took some of the photographs I record with pleasure my special thanks to Mr Reg Prosser. of the Alfred Hospital Pathology Department for his expert preparation of many thousands of microscopical sections, to Mr Frank Watson of the Buckston Browne Research Farm for his preparation of the majority of the microphoto graphs, to my secretary Miss Patricia Leicester, whose efficiency and enthusias

CHAPTER I

DEFINITION OF THMOUR

DEFINITION

Cancer Res reely necessary to state that in this work the word tumour is used in the committed or specific sense of a true neoplasm and not in its ancient rand gard 3 42'of any localized swelling which included also inflammatory and reparative nodsses, hyperplasias, simple cystic swellings and malformations Indeed a m task of this chapter will be to determine in what ways true tumours or neoplasm differ from all of these

In his admirable Erasmus Wilson Lectures in 1925, Nicholson maintaineo that it is impossible to define a tumour. Wherever we look we see that tumou exhibit no differences in kind but only differences in degree—and these often the slightest—from the other tissues of the body. I have tried for years to formu late a definition but have failed. Others have been bolder. I will not weary you with their definitions, every one of which breaks down at one or more points In spite of this deterring statement by one whose knowledge and judgement demand the greatest respect I nevertheless shall essay a definition. I believe that it is possible to frame a satisfactory definition avoiding the grosser defects of some previous attempts, and clarifying by explanatory notes those obscurities which the very brevity of defining creates

A tumour is an abnormal mass of tissue the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the chance

ANALYSIS OF THE DEFINITION

(1) "An abnormal mass of tissue"

The essential tissue of a tumour is the actively growing cells of a specific kind or kinds which comprise the tumour proper, as distinct from incidental cells of other kinds which form the stroma of the growth or which are due to secondary inflammators or phagorytic reactions in it. Thus the essential tissue of a myoma is its muscle fibres - its connective tissue strands and blood vessels are merely the supporting and vascular framework of the tumour tissue proper So also in a malignant tumour for example a scirrhous carcinoma of the breast although wide areas of the growth may consist of much dense fibrous tissue with only scattered groups of epithelial cells there is no doubt that these cells only

nom suffered neoplysticate lings, and that the excessive fibrous tissue results helial tumom for the uterus s in the stroma. In tumours, then as in normal helial tumours of the vaging prenchyma or tumour tissue proper from stroma helial and related tumold vascular tissues

cinoma of the profis the neoplastic tissue consists of cells of a single kind derived dermoid cars, kind of tissue Tumour classification and nomenclature are largely thehal on this fact. Thus a myoma is a tumour whose parenchyma consists of muscle fibres only a chondroma is composed solely of cartilaginous tissue

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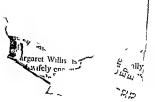
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I greatly lightened the task of preparing the manuscript, and to Mr. W. R. Le Fanus, L. L. Landerson, and L. College and L. L. Landerson, L. La * Librarian to the College, and his staff for much bibliographic help under difficult VIII

for permission to reproduce from my published papers Figs 2-7, 12 13 286, 301 and 302, I am indebted to the Editor of the American Journal of Cancer and of Cancer Research. The Editor of the Journal of Pathology and Bacteriology. and of Cancer Research The Editor of the Journal of Pathology and Bacteriology, Mindly permitted me to reproduce Figs 39-41 167, 189 382 454 464-468 470 Figures 185-188 309 312 and 386 arc eproduced by permission of the Editor of the Medical Journal of Australia An author could not wish for greater consideration and courtesy than my -0\DOV Maj 1947

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uncommon in individual tumours of this kind the majority of myomas grow progressively and often to a huge size. The individual myoma which exhausts its power of growth during the lifetime of the body in which it lives is not thereby to be placed in a different class from all the other progressively growing myomas. In rare cases, even malignant tumours have been known to become quiescent or even to disappear. This, however does not invalidate the all too general rule that untreated malignant tumours grow progressively to a fatal termination and the occasional exceptional tumour is none the less a tumour of the same class as its fellows.

The most distinctive characteristic of a neoplasm is that it retains its property of presistent excessive growth independently of the stimuli which evoked it. There is ample evidence of this, in spite of the defects in our knowledge of the causation of many kinds of tumours. The experimental evidence alone is conclusive. Experimentally produced tumours of every kind may develop long after applications of the chemical or physical carcinogens have been discontinued, and the growth of established tumours proceeds indefinitely without further applications of the carcinogens. This irreversible neoplastic habit of growth, not dependent on the continued presence of the evoking agent is most strikingly apparent with transplantable tumours, for these can be transferred by successive passages to many other animals and yet retain their neoplastic properties unim paired. Cultures of tumour cells in sitro also maintain their peculiar properties and grow into tumours when engrafted into fresh hosts.

So also with human tumours, of those the extrasic causative agents of which are known many develop long after these agents have ceased to act. Mule spinner seancer lung cancer in the Schneeberg miner actinic cancers of the fair skinned farmer or sulor—these may all appear many years after the actims have retired from their hazardous occupations. Of course there are many patients who are still engaged in these occupations at the time when their tumours first appear, but such continuous exposure to careinogenic stimuli is clearly not essential for the initiation of tumours much less for their continued growth once they have developed.

It may be objected that there is no proof that during the genesis and subsequent growth of a tumour the responsible carcinogen has ceased to act but that, for example a careinogenic hydrocarbon may be retained in infinitesimal but effective amounts in the cells of the established tumour evoked by it. A little reflection however will show the untenability of this view. We know from experiments (see Chapter 4) that extremely minute quantities of chemical carcinogens e.g. 0 0004 milligram of dibenzanthracene can evoke transplantable tumours suppose that such minute quantities are retained in the tissues to be distributed indefinitely amongst all the cells of the growing tumour, its metastases and its transplants is to suppose the impossible there would not be enough molecules of the substance to permit of such unlimited distribution Again the genesis and growth of tumours evoked by ultra violet light A rays or other radiations are clearly not dependent on continued applications of rays the actinic or \(\lambda \) ray cancer may appear and progress long after exposure has ceased. It might be argued that the radiations act only indirectly by producing a chemical carcinogen in the tissues and that it is this which persists in and maintains the growth of the resulting tumour, but this, of course, is the same impossible supposition as we have just rejected

It is clear that tumour growth ennot be conceived as being maintained by the continued stimulation of the tumour tissue by the same agents as evoked it. These agents must act by initially inducing in the cells irreversible changes of metabolism and proliferation, which are then transmitted indefinitely to the descendants of the initially changed cells—in the primary tumour, in its metastises, in transplants and in explants in into. The nature of these changes, the very essence of the neoplastic reaction, is still unknown, it is discussed further in Chapter 11

DEFECTS OF SOME PREVIOUS DEFINITIONS

Some previous definitions of tumour have failed in that they have omitted the all important characteristic of continued disproportionate growth independent of evoking stimuli. Thus Powell White s definition adopted by both Adam and Kettle, defined a tumour as a 'mass of cells, tissues or organs, resembling those normally present in the body, but arranged atypically, which grow at the expense of the organism without, at the same time, subserving any useful purpose therein. Because this definition said nothing of a tumour s progressive disproportionate growth, it failed to distinguish tumours from malformations to all of which it was perfectly applicable. Failure to make this distinction has led to the unwarranted inclusion of a number of simple malformations amongst tumours an error which is discussed further below.

The unlimited disproportionate growth of tumours has led many writers to infer erroneously that tumours possess complete autonomy and are exempt from the laws of normal growth. Thus MacCallum's definition includes the statement that tumours grow without any regard for the laws which govern and restrain the growth of normal tissues and it has often been asserted that tumours grow without control ' in an anarchic manner, 'lawlessly' or ' as parasites ' Ewing defines a tumour as "an autonomous new growth of But as Nicholson (1921) so emphatically insisted and as Foulds (1940) has more recently repeated the orderly architecture and functional activity of many tumours refute such views Again Nicholson (1933) pertinently said, "It is all very well to prate of the laws of normal growth which are transgressed' by autonomous tumours But it would be better still to enumerate these laws. to show how they are enforced in normality and in morbid states in which there is no autonomy of the peccant part, and above all to decide on the guilty party when they are broken Tumours are neither lawless nor autonoin the sense that they obey peculiar laws of their own. The idea that tumours are "lawless' anarchic or "parasitic' clearly arises from too exclusive a view of the malignant tumours of rapid growth poor cellular differentiation and destructive effects. These malignant qualities obtain in only a proportion of tumours and then in very variable degrees The terms autonomy" as applied to tumours are indeed but figurative ways of expressing their main characteristic, namely, their continued excessive cellular

proliferation, not dependent on continuance of the initial carcinogenic stimulus It is this only that constitutes their anarchy?

HOW TUMOURS DIFFER FROM OTHER PROLIFERATIVE LESIONS

To clarify still further our concept of a true tumour it will be helpful to state briefly how tumours differ from (1) inflammatory and repartitive proliferations, (2) hyperplasms, and (3) malformations with excess of ussue

(1) How tumours differ from inflammators and reparative preliferations

Reparative proliferation of cells either in purely reparative processes or in association with inflammatory changes clearly has a useful function namely repair. This is most evident in simple healing lesions such as a clean granulating wound or a uniting fracture but in chronic inflammatory lesions also like those of tuberculosis or syphilis the newly formed tissue though frustrated in its reparative function and itself damaged by the persisting microbe is still of reparative value for if the parasite is eliminated this tissue promptly completes the healing of the lesion. It may be remarked in parenthesis here that to say that inflammation and repair are functionally useful' does not commit us to any narrow teleological view any more than to say that the function of the liver in secreting bile is useful. All that is implied in these statements is that the processes in question contribute to the prescriation and health of the organism In this sense reparative proliferation has value, while neoplastic proliferation has not. The cellular multiplication of reparative tissues, unlike that of tumours is not progressive and continuous but is limited by the extent of the breach to be filled or the duration of the tissue damage evoking it

(2) How tumours differ from hyperplasia

The usual definition of hyperplasia as an abnormal increase in the cells of a tissue (as in Webster's dictionary or Gould's medical dictionary) is too broad to be useful it includes for example all tumours. If the term is to have value in pathology its meruing must be restricted and clearly specified as follows. Hyperplasia is the proliferation of the cells of a tissue either (a) as a compensatory response to loss of tissue of the same kind or to increased functional demands which the normal amount of tissue cannot satisfy, or (b) as a result of disturbed hormonal control of the activity of the tissue.

Examples will make these meanings clear. If liver tissue is lost either by excision or by damage by poisons new liver cells are freely produced by mitotic profileration from surviving liver tissue. Similarly loss of kidney tissue by removal or disease is followed by increase in bulk of the remaining renal tissue by prohiferation of the epithelial cells of surviving tubules. Removal of part of in endocrine gland is commonly followed by proliferation of the cells of the remainder so that the normal amount of the tissue is almost or quite restored. In anaemias increased erythropoiesis is seen in the hyperplastic red bone marrow, while in inflantmatory diseases with leucocytosis the leucopiotic cells of bone marrow show hyperplasia. Compensatory hyperplasias are allied to repair from which however they differ in the specificity of the regenerated cells and in the fact that the regeneration is not restricted to the immediate site of tissue.

loss The function of repur is to fill a breach, the function of regenerative hyperplasia is to compensate for the loss of cells of a specific kind

The second type of hyperplasm, that due to disturbed hormonal activity, is exemplified in the ductiess glands themselves and in organs whose functions and structure are under hormonal control, such is the breast, interus and prostate. These hyperplasms include such familiar lessons as goitres, cystic and lobular mastopathy, various endometrial overgrowths including endometriosis, and benign prostatomegraly. In some of these the nature of the responsible endocrate disturbance is known in others it is still obscure.

Hyperplasias of both kinds differ from tumouts in that the proliferation is limited in amount and duration, it progresses only so long as the functional need or hormonal stimulus which evoked it persists. Hyperplasias of the regenerative or compensatory type also of course differ radically from tumours in possessing functional value, this is their very raison d fire

That neoplast 1 may supervene on hyperplasm a subject to be discussed in Chapter 7 does not any lidate, but serves rather to emphasize, the distinction between the two If in a hyperplastic tissue, proliferation becomes excessive and independent of persistence of the stimulus which induced it then we recognize that a new quality in the proliferation, that of neoplasia, has supervened

(3) How tumours differ from malformation with excess of tissue

By a malformation I mean an anatomical error arising in the course of development of the body to its adult state. As might be expected, the embryonic stages of development, when the greatest structural changes are in progress are the most productive of developmental errors more so than the later foetal or infantile stages, when architectural moulding is less in evidence than growth in size (see Ballantyne, 1902). Hence most malformations are congenited they have arisen from disturbances of embryonic or foetal development. Many of these are already elimically apparent at birth, others do not make their clinical appear ance until later but are nevertheless present in proconspicuous form at birth.

It is, however, a mistake to assume that all malformations are congenital, for quite apart from mere growth in size, the developmental modelling of organs and the differentiation of tissues are not complete at birth. A child is not a tiny adult, many of its parts are still immature and in process of genesis. Thus adult structure is clearly not attained in the gential system until after puberty in the skeleton until the ceptibyses are untiled, in the paws until the permanent teeth are erupted, and, microscopically, complete differentiation of renal tissue, sympathetic ganglia and some endocrine tissues is not attained until some years after birth. The structural immaturity of many parts in childhood and adelescence is as it were, a projection of embryonic and foetal development into post initial life, and in such parts minor malformations theoretically may and in fact do, sometimes arise from disturbances of post initial development.

While the term 'malformation' thus legitimately includes not only errors of development present at birth but also those due to disturbances of the post natal development of tissues still immature its meaning should not be extended to embrace anomalies of structure acquired after indulthood of the affected tissues has been attained. It is true that our tissues and organs change throughout life,

and that in this sense development continues until death, but in the more usefully restricted sense, development of a part is complete when it is fully formed or shaped to the adult pattern. After this although it may vary in size and structure for functional or nutritional reasons and although it may suffer various kinds of injuries to which it may react in various ways, it can no longer suffer developmental malformation in the usefully restricted sense of that term. Lesions acquired after attainment of the adult state of a part represent disturbances, not of development but of maintenance, they are detormations not malformations. I cannot subscribe to Nicholson's view (1921 and 1926) that tumours generally can be looked upon as malform tions.

Malformations which involve no excess of tissue such as absence or deficiency of parts, and arrest of development such as eleft palate or imperiorite anus of course cannot be metaken for timmours. Even many malformations with excess of tissue such as supernumerary or grant digits accessory splicens or duplicated ureters, cannot be confused with tumours. Such confusion has occurred most frequently as regards those malformations in which the virtous tissues of a part are present in improper proportions or distribution with prominent excess of one particular tissue. Such tumour like malformations, designated by Albricht (1904) "hamaritoms, include most angiomas, beingin pigmented moles most of the neurofibromatous masses of von Recklinghausen's disease and the cartilage capped multiple evostosis. All of these will be diseased in due course here the common angioma or birth mark will serve as an example

That the ordinary eutaneous angioma, such as the port wine stain, is a maiformation and not a tumour will be clear from the following facts. It is present at birth at grows only with the growth of the rest of the body, and does not extend to involve a greater and greater territory of tissue—after growth ceases it usually remains unchanged for the remainder of life unless accidents such as trauma thrombosis haemorrhage or infection take place in it. Briefly, it has no disproportionate or progressive powers of growth. Further no sharp distinction can be drawn between the commoner varieties of angioma and the rater plexiform or racemose angioms. Cirsoid aneurysms, and widespread angiomatoid dilatation—of the vessels of the central nervous system or elsewhere, and these rarer forms are clearly only vascular millormations.

The growth of a multormation differs fundamentally from that of a tumour in that it is limited and co ordinated with that of the rest of the body. The ordinary angional enlarges only pair passa with the part of which it is a blemish, then stops, it does not extend beyond the territory originally involved. A pigmented mole, though it displays a stage of youthful development, remains restricted to its particular field of origin and usually exhibits later retrogressive sense, entendinges. The growth of cartilage-capped exostoses ceases when the cartilage undergoes complete ossification about the period of union of the epiphysis. In short, malformations have no powers of excessive uncoordinated growth.

Finally however it must be noted that there are certain tumours which are also malform thous, the teratomas and the true embryonic tumours. While these are clearly neoplasms, often malignant neoplasms they also conform to our strict definition of malformations as material errors arising in the course of the body to its adult state. They are disturbances of development of immature

tissues involving their neoplastic conversion, and there is little doubt that this is due, not to the application of any extraneous careinogenic substance, but to disordered chemistry in the tissues themselves during their embryonic growth Actiologically is well as structurally, then, these neoplastic malformations differ from the much commoner tumours acquired in later life

CONCLUSION

The most distinctive character of neoplastic proliferation is that it is uncoordinated independent of the structural and functional pattern of the organism, and indefinitely progressive. In this, it differs fundamentally from reparative growth hyperplastic growth and the growth of malformations in all of which the cellular multiplication is limited in amount and duration in accordance with more or less clearly specifiable factors. It is clear that neoplasia involves some permanent cellular change manifesting itself in excessive multiplication, that this change is transmitted to the descendants of the first affected cells to an indefinite number of generations and that it persists in these without continuance of the stimuli which initially evoked it

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CHAPTER 2

CLASSIFICATION AND NOMENCLATURE

THE OBJECT of any classification is to arrange a collection of diverse things into named groups and subgroups of similar or related individuals. The individuals composing a group are not usually replicas of each other, but they resemble one another more closely than they resemble those of other groups system is convenient indeed an indispensable aid to thought but its inherent Immations must be clearly recognized Especially in biological subjects sharp separation of groups of individuals is not possible the different classes which we create and name though convenient are not distinct in any absolute sense Just as the systematic botanist or zoologist recognizes that living creatures in each group show such a range of variation that the boundary lines between related genera and species and between species and varieties are often difficult to define so also the pathologist must recognize similar intrinsic difficulties in the classification of tumours. The individual tumours of each main group exhibit a great range of structure and behaviour so that sub divisions within the group like those of species within a genus, are largely arbitrary. Unfortunately here as in other fields of thought once we have given a name to such an arbitrarily determined group we are apt to forget its arbitrary character and to accept the name is denoting a specific entity. Further, some names in current use perpetuate erroneous hypotheses regarding the origin and nature of certain tumours. Perhaps pathology more than most branches of biological science suffers from this tyrinny of names

In framing our classification and terminology of tumours then we should be guided by the following two rules

- (a) Our grouping should be simple and basic avoiding as far as possible the creation of artificial arbitrary sub divisions
- (b) Our nomenclature should be simple and precise excluding all names of erroneous or doubtful meaning or where common usage necessitates their retention for the time being indicating their defects and suggesting preferable substitutes.

The multiplication of new names should be avoided in my opinion the familier terminology in current use affords enough suitable names for our purposes, the mening of each name employed however must be made precise and clear

HISTOGENETIC CLASSIFICATION

Unquestionably the fundamental basis of scientific classification is histogenetic that is according to the tissues from which tumours arise and of which they consist. As we have already noted in Chapter 1 the essential parenchyma of a tumour consists in most cases of cells of a single type derived from one only of the tissues of the body clearly the tumour should be named and classified according to the nature of this tissue. As Mallory insisted. Tumors are classified like normal tissues on a histologic basis. The type of cell is the one

important element in every tumor From it the tumor should be named, not from some peculiarity of minor importance, such as method of growth or arrangement of cells, or form of retrograde change?

Microscopical identification of the nature of a tumour depends on the recognition of the kind of cells composing it. When the cells are well differentiated, as they often are in slowly growing tumours, a microscopical diagnosis of the nature of the tumour is usually easy. When growth is rapid, however, cellular differentiation may be very imperfect or entirely wanting and microscopical identification of the specific nature of the tumour may then be difficult or impossible. With increasing experience the histopathologist learns to recognize those slight degrees of differentiation in tumour tissues which clude the beginner. Sometimes also an otherwise undifferentiated tumour may contain scanty areas with sufficient differentiation to permit specific diagnosis, but prolonged search may be necessary to find these.

The following example will serve to illustrate the variable degree of differ entiation, and therefore of specific histological identification, possible in tumours all of the same origin A circinoma of the thyroid may, in parts, present almost perfect differentiation of unmistakable thyroid vesicles filled with colloid secretion. so that from histological study alone a confident diagnosis of "adenocarcinoma of thyroid tissue can be made. Sections of a second thyroid earcinoma may exhibit well marked glandular architecture but without the formation of recognizable thyroid vesicles or colloid, so that the histologist can identify the growth as "adenocarcinoma", but cannot assert its thyroid origin Sections from a third carcinoma of the thyroid may display clear evidence of its epithelial nature in the grouping of its cells in circumscribed compact clumps but may be devoid of any glandular orientation of the cells, the tumour can then be identified no more specifically than "carcinoma' Finally, a fourth tumour may be so lacking in differentiation that even the epithelial nature of its cells cannot be inferred from its structure or arrangement, the histologist alone can identify it then only as "a highly cellular anaplastic tumour of undetermined origin while all four tumours are of the same kind namely 'carcinoma of the thyroid', the precision of histological identification which is possible varies from tumour to tumour, and this is reflected in nomenclature. It may be noted here that a single tumour may display in different parts all these varieties of structure so that the degree of precision of the histological diagnosis will depend on the part of the tumour examined a point which is often overlooked in attempts to assess the relative malignancies of different tumours in one class

There occur tumours corresponding to almost all kinds of normal tissues, and clearly our classification of tumours will run parallel with our clissification of normal tissues. Just as the histologist may conveniently group these tissues into several main classes—such as epithelia of various types, non epithelial (connective, vascular, skeletal, muscular and haemopoietic) tissues nervous tissues, etc—so the pithologist may group tumours into corresponding main classes. In a general way the prevailing nomencleture of tumours, although defective in some respects has followed this course.

The histogenetic classification of tumours encounters difficulties of two kinds (a) those due to lack of precision in the histological classification and naming of normal tissues, and (b) those due to uncertuinty regarding the tissues of origin

of some kinds of tumours. Difficulties of the former kind must be resolved by the unatomist and embryologist and of the latter kind by the pathologist

(a) Lack of precision in histological nomenclature is well exemplified in the usage of the familiar name epithelium. While everyone agrees that this properly applies to the epidermis the lining cells of visceral mucous membranes of all kinds, and the secreting cells of glandular derivatives of these whether exocrine or endocrine, there is still disagreement as to whether the cells lining the serous and vascular cavities should be called enithelia. That these cells have little in common with those of the epidermis and sisceral linings has been recognized by both anatomists and pathologists. As long ago as 1865 His proposed to distinguish the filse from the true enithelia by calling the former endothelia later Minot suggested that the term mesothelium should be used to distinguish the coclorus cells from the vascular endothelium. While this practice has been followed by many histologists (e.g. Bremer and Weatherford and Bloom) most pathologists continue to call both coclomic and vascular linings endothelium. Agun while all agree in applying the term, epithelium." to the parenchyma of those endocrane glands which develop as outgrowths from enthelial surfaces namely the anterior part of the pituitary the thyroid, para thyroid and islets of Langerhans histologists are rejuctant to call the adrenal cortex or the interstitual cells of the testis by this name. Neither Maximow and Bloom nor Bremer and Weatherford use the word epithelium in their descriptions of the adrenal cortex though the latter refer to the enithelioid eells and Maximon and Bloom speak of the interstitual cells of the testis as epithelioid room for doubt as to the propriety of speaking of ependyma as an enithelium . and some histologists might even disagree with Bremer and Weatherford in referring to the cells of the pincal glands as epithelioid. These uncertainties in histological nomenclature have been reflected in pathology e.g. tumours supposed to have arisen from coelomic lining cells have been called carcinoma.

chdotheliom mesotheliom and serosal epithelioma (see Kaufmann 1929) the difficulty of classifying many thymic tumours has led to wide use of the non-commutant anime thymoma and most pathologists have preferred to speak of interstitial cell tumours of the testis. Tather than to designate them as adenomas or carcinomias on the other hand it is usual to refer to adrenal character which as we have seen many histologists frankly do not endorse. These and other difficulties arising out of purely histological considerations will be dealt with each in its appropriate place in this work.

(b) The second difficulty in histogenetic classification namely that due to uncertainty regarding the precise tissue of origin of some kinds of tumours is not a very serious one. It now obtains with only a few kinds of tumours and these will certainly diminish in number as histopathological research advances. The overy remains the most perpleuing region as regards the derivation of many of its tumours parily because of the great variety of tumours observed in this organ not a few of which consist of tissues not recognizably like any of the normal constituents of the overy and partly because of uncertainty regarding the histogenetic relationships of normal tissues in the overy in which it now appears probable stromal and epithelial elements may be intermutable. The teratomas

comprise another group of neoplasms of undetermined histogenesis, but recent progress in experimental embryology and in the study of teratomas promises to discover ere long the nature and mode of origin of these growths

Criticisms of the histogenetic basis of tumour classification such as MacCallum's (1940), are groundless. MacCallum wrote. Classification is at best unsatisfactory on a histogenetic hasis since so often we cannot make a good guess at the tissue which the tumor most resembles or the point from which it actually spring Such a statement from an experienced pathologist is incom prehensible. On the contrary, the evidence for the origin of tumours from their specific normal counterparts is for most classes of neoplasms, precise and conclu good guesses ' are unnecessary It is true that there remain some small groups of tumours the tissues of origin of which are still uncertain. As we have seen, it is also true that some individual tumours in any of the main groups of neoplasms are so anaplastic that histological recognition of their identity is not But neither of these is a valid reason for denying histogenesis as the obvious and essential basis of tumour classification. MacCallum was moreover inconsistent for his arrangement of tumours into twelve groups was basically histogenetic. He insisted that this was 'an arrangement, not a classification', but what is a classification if it is not an 'arrangement"?

BEHAVIOURISTIC CLASSIFICATION INNOCENCE AND MALIGNANCY

In addition to the fundamental histogenetic classification by which tumours are grouped solely according to the kinds of tissue from which they spring and of which they consist, it is also necessary to have a further grouping biologically less fundamental but of great practical value, according to their behaviour and clinical progress

The tumours of any given cell type may show a wide range of behaviour in their rates of growth, powers and modes of spread and degree of danger to their victims. Some grow only slowly, remain quite local do not invade neighbouring tissues, and cause no harm except by virtue of their position or some accidental complication, these are benign or immovent tumours. Other tumours of the same cell type grow rapidly, invade neighbouring tissues spread by metastasis and, unless extirpated at an early stage, inevitably prove fatal these are malignant tumours. Between these two extremes however, many of the histogenetic groups contain tumours of intermediate or borderland behaviour, so that sharp division into imnocent and malignant species is not possible. Innocence and malignancy are relative terms used to make a convenient but arbitrary separation of members of any particular histogenetic series into two sections according to those biological characters which are of greatest significance for prognosis. This subject is discussed at greater length in the next chapter.

Some writers notably Muir (1941) while appreciating the importance of histogenesis have unduly stressed the distinction between innocence and malignancy by making it the primary step in their classification. Thus Muir adopts the primary division of tumours into innocent "Histomata or tissue tumours' and malignant Cytomata or cellular tumours'. This plan is unfortunate, it over emphasizes the behaviouristic hasis of classification by the use of two misleading and unnecessary names. To call a tumour a cytoma' rather than a

"histiom i' is in effect to say that it consists of cells but not of tissue, a statement which save for its possible application to the extremest instances of analysia, is clearly filse. Muir presumably does not intend this literal meaning to be attached to the terms although he specifically translates them as meaning 'tissue tumours' and 'cellular tumours' respectively. The intention is to express in terminology the fact that innocent tumours usually exhibit a high degree of histological differentiation and so resemble the corresponding normal tissues, while malignant tumours often show analysis of various degrees. But there are better ways of expressing this than by introducing two questionable words as the very basis of classification, and moreover, many malignant tumours are highly organized.

While no fundamental distinction can be made between innocent and malignant tumours the distinction for practical prognostie purposes can be made micro scopically in the majority of cases. This applies particularly to some of the commonest groups of tumours, notably to most epithelial and to many tumours of the non epithelial mesodermal tissues. Thus there is usually no histological difficulty in pronouncing a tumour of glandular origin to be either a benign adenoma or a malignant carcinoma or in distinguishing an innocent lipoma. osteoma, or leiomyoma from the corresponding malignant sareoma papillary epithelial tumours not infrequently exhibit borderline behaviour and so render histological prognosis difficult and the same applies to some fibromatous and chondromatous tumours. As regards the tumours of neural tissues. especially the common gliomas sub division into innocent' and ' malignant' classes is quite arbitrary and serves no useful purpose for these tumours show all possible gradations between slowly growing well differentiated types and rapidly growing anaplastic types and even the former are infiltrative in their mode of growth Some other groups of tumours, e.g. melanoma ehordoma, chorson epithelioma and embryonic tumours of viscera are always to some degree malignant and have no really benign counterparts so that behaviourist sub division of these groups is not ealled for

IMPROPER BASES OF CLASSIFICATION

It is necessary to consider here in order to discard certain other bases which have been used in classifying tumours These are (1) regional, (2) embryological, (3) actiological

(1) Regional classification

To a certain degree histogenetic classification is of course regional. Gliomas can arise only in the central nervous system myelomas only in bones, chordomas only in the spinal axis and so on Again innocent epithelial growths often possess such distinctive histological structure that this alone permits identification of their specific regional origin e.g. papillomas of the urinary tract or of the large intestine or adenomas of the breast or thyroid. Even some carcinomas possess a microscopical structure pointing unmistakably to their specific site of origin this applies not infrequently to curcinomas of the kidney, thyroid and liver and occasionally to curcinomas of the prostate uterus and intestine. Further, tumours of similar histological type may exhibit different behaviour according to their

different sites of origin, e.g. epidermoid circinomas of the skin, lip or larynx are in general slower in growth and later to metastasize than epidermoid carcinomas

of the tongue, pharynx or oesophagus

Apart from these features, which are essentially related to histogenesis, regional grouping of tumours has little vilue. Any organ or system of the body consists of a variety of tissues each of which may be the source of tumours of its own kind. The tumours of a particular kind of tissue are unlike those of other tissues in the organ but closely resemble m structure and behaviour tumours of that kind of tissue in any other organ or region of the body. Thus a carcinoma of the intestine has much in common with carcinomas of the stomach, lung or breast, but his very little in common with a myoma, or a neurofibroma, or a lymphosarcoma of the intestine. It is the tissue of origin not the organ of origin, of a tumour on which its peculiar properties depend

(2) Embryological classification

The best known ritempt to classify tumours on an embryological basis was that of Adami (1909). He distinguished 'teratomata' derived from totipotential' cells, 'teratoblistomata' or mixed tumours derived from 'nultipotential' cells, and blastomata' derived from 'unipotential' cells. The blastomata' derived from 'unipotential' cells. The blastomata' bedivided into two main groups, "lepidomata" (membrane tumours) and hylomata' (pulp tumours) corresponding to epithelial and non-epithelial tumours. These were sub divided into 'epilepidomata, ly polepidomata and mesolepidomata and 'epihylomata, hypohylomata and mesolepidomata', according to the germ layers from which the various tissues of the body arise. In each of these sub divisions typical' and "atypical" (corresponding to innocent and malignant) tumours were distinguished. Thus a benign papilloma of the skin would be a typical epilepidoma', a careinoma of the colon would

be an 'atypical hypolepidoma", and a surcomu would be un "atypical mesohyloma"

Although Adami's scheme was widely quoted, it had no real ment duced a series of new names with no advantages over the corrresponding old ones, and it laid a wholly unwarrantable emphasis on the germ layer derivation of the tissues from which tumours arise From skin, oesophageal mucosa and the uterine cervix, which are clothed by squamous stratified epithelia derived from ectoderm, entoderm and mesoderm respectively, there arise epidermoid carcinomas of closely similar structure and behaviour. To designate these as three separate classes of tumours epilepidomata hypolepidomata and mesolepidomata according to the early germ layer origin of the respective tissues is to create artificial distinctions devoid of pathological value or meaning. Worse still, application of this nomenclature in certain regions leads to the artificial cleavage of a homogeneous group of tumours of a single organ Thus, squamous celled carcinomas of the anterior two thirds of the tongue, which is ectodermal, would epilepidomata ', while identical carcinomas of the posterior third, which is entodermal would be "hypolepidomata", and so also papillary growths of the fundus and of the trigone of the bladder would be distinguished as "hypo lepidomata and mesolepidomata' respectively. The female external genitalia contain stratified epithelia derived from all three germ layers so that squamous celled carcinomas of the labia majora would be epilepidomata similar gro vths

of the labri minora would be hypolepidomata, and similar growths of the vagication orifice above the level of the hymen would be mesolepidomata. Such distinction are clearly meaningless. Indeed the germ layers the status of which has of rece as part greatly declined even for the embriologist ore devoid of significance for perty pathologist. Ewing (1940), discussing Adams classification rightly concluded the behaviour of tumor cells is very much more influenced by the receive characters of the cells of origin than by their embryological derivation. The neophistic process does not consist in retraeing the steps of embryological declosed by ment. Oncology is not a department of embryology but a septrate chapter in the control of the c

In other minor ways embryological concepts have been improperly introduced sometimes deliberately and sometimes unwittingly, into the nomenclature are classification of tumours. Thus it has become a prevalent habit to replace it familiar ending oma by blastoma the usual intention being to suggesces that tumours consist of young proliferating cells of this or that type. Thus taggs term fibroblastoma is used to embrace all of those tumours fibromas at II fibrosarcomas which arise from and represent fibrous connective tissue cell be At first sight there may seem little to cavil at in this usage especially as commonly use the name fibroblast to apply not only to immature connecti issue cells in the embryo but to proliferating connective tissue cells in granulatic tissue and other proliferative lessons in adults. So also we speak of osteoblast ness

lymphoblast myelobiast and so on in reference to proliferating cells of the difference to see that to such names as osteoblastoma or lymphoblastomal strong objection can scarcely be sustained. As regards certain other cell types however the blast ending has a specifically embryological significance. Thus the name spongioblast refers to immutute embryonic precursors of neuroglad cells. Hence to describe a tumour composed of incompletily differentiated neuroglad cells as a spongioblastomal is to imply embryonic derivation and properties when only amplitudes as properties when only amplitudes to other names in the Builey Cushing classification of brain tumours—astroblastoma.

ependymobhstom and pinealoblastom. So also the term myoblast refers specifically to embryonic muscle formative cells—so that the wisdom of using the name myobhstom for a tumour derived from adult muscle is open to question.

These objections to a too field use of the ending blastoma' are all the more cogent because of the existence of certain truly embryonic tumours derived from and composed of immuture tissues which have never attained adulthood namely the embryonic tumours of the kidney adrenal and sympathetic system retina liver etc. These are properly given such names as incphroblastoma.

neuroblistom; sympathicoblistoma retinoblistoma and hepito blistom; because they actually do consist of embryonic renal sympathetic, retinal or knatic cells as the case may be

retinal or acpatte cells as the case may b

(3) tetrological classification

the biology of the cell

Twing MacCillum and other pathologists have expressed the belief that any time the work of the curvation of tumours will permit more scientific classification. MacCillum even goes so far as to deny the wisdom of attempting

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diffessification on any other basis than aetiology, and he makes the strangely are orrect statement that we know nothing of this. That better knowledge of tusation will afford a basis for classification is a vain hope, because (a) a variety.

of tusation will afford a basis for classification is a vain hope, because (a) a variety "Afferent carcinogenic agents may evoke identical tumours, and (b) a single groutinogenic agent when applied to different tissues, may evoke a variety of of anotes. This carcinomas of the skin indistinguishable from one mother as Thigards their structure and behaviour may be produced experimentally by the ortsplication of such diverse agents as ultra violet light, X rays, arsenic and a tissent variety of carcinogenic hydrocarbons. On the other hand, a single carcino hamile hydrocarbon suitably applied is capable of evoking such diverse growths ver squamous celled carcinoma of the skin, adenocarcinoma of the kidney, the roomas of soft tissues, osteogenic sarcoma of bone and cerebral glioma (see its papter 4)

In this respect tumours differ radically from inflammatory diseases. In these, h kind of microbic parasite calls forth its own peculiar tissue reactions, and, h variations the resulting disease runs its peculiar course. Hence inflammatory of Acases are properly classified on the basis of their causation. For tumours, cells sever no specific relationships between the nature of the external agents and and tissue reactions evoked, the tumours, are apparent. The neoplastic change divising given tissue possesses qualities which are largely, if not wholly, independent

h the kind of stimulus responsible for it Causation then can never afford a basis

tunr the classification of tumours

COMPOUND NAMES

Much confusion has been caused by the use of ill advised compound names for certain tumours. Compound and hyphenated names have been used in three distinct ways and in employing such a name it is important to recognize clearly in which of these three ways it is being used.

- (a) Compound names have been used purely descriptively to enumerate the different components or variants seen in the tumour. Thus, in less enlightened days, a teratoma containing muscle, cartilage and glandular tissues might be called a 'rhabdomyo chondro carcinoma, or a sarcoma of bone of pleomorphic structure might be called an osteo myxo chondro sarcoma. The dements of such stringing together of names are obvious, they are clumsy, unnecessary, and have all too often carried an implication of multiple histogenesis which was quite erroneous or fanciful. Thus the pleomorphic salivary tumours have been called 'chondro myxo haemangio endothelio sarcomas'.
 - (b) Compound names such as 'adenocarcinoma" or fibrosarcoma" are properly used with an intention quite different from (a), the first part of the name is an adjectival prefix descriptive of the second. An adenocarcinoma is not a mixture of adenoma and carcinoma but a carcinoma in which structural evidence of glandular characters is seen And a fibrosarcoma is not a mixture of fibroma and sarcoma, but a sarcoma of recognizably fibroblastic derivation and structure
 - (c) The third way in which compound names are constructed is to

designate genuinely compound tumours. Thus a mammary fibro adenomy consists of two distinct neoplastic tissues a fibromatous component and an adenomatous component both equally demanding recognition in naming the tumour. So also those very fare tumours in which malignant epithelial and non epithelial tissues coexist are properly called 'carcino sariomas. The necessity of having compound names of this kind makes it all the more imperative, to avoid the bad habit of inventing those of type (a). I suggest that the names of truly compound tumours should be distinguished from compound names of variety (b) made by the mere addition of prefixes by using a hyphen for the one class but not for the other, as has been done in these paragraphs

THE CLASSIFICATION ADOPTED

The following grouping based solely on histogenesis and behaviour embraces all the usually recognized classes of tumours without involving any great changes in existing nomenclature, and it indicates the order of presentation in Part II of this work in which its defects and inevitable points of overlapping will be pointed out

(1) Group I Tumours of epithelial tissues

If benign these are papillomas or adenomas, if malignant careinomas (Names such as adenocareinoma 'squamous cell careinoma careinoma simpler' etc., do not denote different species but merely variations of structure with respect to kind and degree of differentiation)

(2) Group II Fumours of non-haemoposetic mesenchymal tissues

Beingn tumours of the connective skeletal vascular meningeal and museular tissues are fibroma, myxoma lipoma chondroma osteoma, beingn osteoclastoma, synoxioma angioma (heam ingioma liymphangioma, glomangioma) meningioma, leiomyoma and rhabdomyoma Malignant members of the same classes receive the generic name sarcomi often with a prefix corresponding to the beingn counterpart

(3) Group III Tumours of haemopoietic tissues

The peculiar nature of the haemopoietic tissues and their tumours especially their production of freely circulating or mobile cells justifies separation from those of the fixed mesenchymal tissues. These tumours are conveniently grouped thus

- (a) Tumours of lymphoid tissue
 - (i) Follicular lymphoma
 - (ii) Lymphosarcoma and lymphatic leukaemia
 - (iv) Reticulosarcoma
 - (iv) Reficulosarcoma
- Myelomatosis and plasmocytoma
 Myelogenous leukaemia and chloroma
- (d) Primary polycythaemia

(4) Group IV Tumours of neural tissues

This is a diverse group comprising

(a) Ghomas

- (i) Astrocytic gliomas (astrocytoma and "glioblastoma")
- (11) Oligodendroglioma
- (iii) Medulloblastoma
- (iv) Ependymal glioma (v) Pinealoma
- (b) Papillary tumours of choroid plexus
- (c) Neurilemmoma
- (d) Neuroblastoma and ganglioneuroma
- (e) Chromafinoma and carotid body tumour
- (f) Retinal and ciliary tumours
 - (i) Retinoblastoma
 - (u) Diktyoma
 - (iii) Enthelial tumours of the ciliary body

(5) Group V Sundry special classes of tumours

- (b) Melanoma
- (a) Chordoma
- (c) Embryonic tumours of viscera
 - (i) Nephroblastoma
 - (ii) Hepatoblastoma
 - (iii) Embryonic tumours of other parts
- (d) Teratomas
- (e) Chorion epithelioma

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CHAPTER 3

INNOCENCE AND MALIGNANCY

"INNOCENT' AND "MALIGNANT RELATIVE TERMS

THE PREVIous chapter admitted the necessity of a behaviouristic sub-division of several of the histogenetic groups of tumours, but stressed that the distinction between innocence and maligraney is not fundamental or clear cut. This chapter is to amplify our conceptions of this distinction the arbitrary nature of which may be made apparent at the outset by the following considerations.

(1) Borderline tumours

Miny histogenetic species of tumours include some growths which occupy the borderline between innocence and mitiganary. Good examples of this are villored by papillary epithelial growths many of which cannot be classed with precision either as beingn papillomas or malignant papillary circinomas. Thus the papillary growths of the bladder exhibit a complete range of structure and behaviour—from the slowly growing wholly superficial pedimeulvick villous papilloma of uniform fully organized architecture, to the rapidly growing, infiltrature, sessile, irregularly papillary carcinoma. Of many of the intermediate members of such a series, it is difficult to assess the degree of maligrancy and to predict their probable course. Some growths with a past history and microscopical structure which lead us to look upon them as beingn, may nevertheless prove their essential malignancy by later recurrence infiltration or nicitatives. Similar borderline charactures are displayed by some of the papillary growths in the microscopic horderline behaviour will be deserbed in detail in later chapters.

(2) "Black sheep" in innocent families

Some species of tumours generally looked upon as benign nevertheless include occasional malignant members. Good examples are the osteoclastomis of bone the slowly growing salivary tumours the ecchondromas and the leomy omas. On rire occasions tumours of these kinds though chineally and histologically differing little or not at all from their innorent fellows surprise us by metastistizing and their metastrase may present an innocent histological structure. Writers have sometimes described this anomalous and unexpe ted behaviour by using the self-contridictory phrise. metastasis of benign tumours' (e.g. Lwing 1940). So also Colinheim and others long aco described as sample colloid goitte with metastases examples of disseminated growths with a nicroscopical structure closely resembling normal or goitrous thyroid tissue. It need scarcely be said now that such terms are incorrect and misleading metastasis is conclusive evidence of malignancy no matter how slow the growth or how well differentiated the structure of a tumour. (See discussion of ' benign metastasising pourter by Bell and Sampson.)

(3) The supervention of malignancy in benign tumours

Related to the foregoing characters is the apparent development of malignancy innocent" tumours. Thus in a previously benign myoma of the uterus a sarcoma may arise, or a seemingly quiescent thyroid adenoma many years old may finally yield widespread metastases in lungs and bones. or a simple polypoid papilloma of the colon may undergo carcinomatous transforma While in some cases such as these it is clear that a genuine change from innocent to malignant characters has taken place in the tumour, there are other cases in which this interpretation is open to doubt and it is more probable that the growths possessed low grade or borderline malignancy from the beginning In discussing this problem as long ago as 1906, Bland Sutton well said, 'It is so difficult to decide between the slow growing spindle cell sarcoma, the fibrifying sarcoma and the gelatinous fibroid (myoma), that it is unwise to argue from our present knowledge that innocent connective ussue tumours may undergo transformation into sarcomata The more carefully the histology of tumours is investigated the more obvious does it become that the borderland between innocent and malignant species becomes less easily definable." As later sections of the present work will show, however, indubitable examples of the supervention of milignant change in previously benign tumours do occur, and these, no less thin the borderline tumours which Bland Sutton so rightly emphasized, also illustrate the purely relative meaning of the terms ' innocent and " malignant'

The over emphasis which has been placed on the distinction between innocence and malignance has arisen because of the prognostic value of this distinction. The clinician is first demand of the pathologist who examines the tumour he has removed is Is it innocent or malignant?" This habitual query has engendered the notion that every tumour must be either innocent or malignant. A more enlightened modification of the question and one which rathologists should encouring clinicians to ask is Most innocent or malignant is this tumour?"

INNOCENCE AND MALIGNANCY CONTRASTED

Fortunitely the distinction for practical purposes between innocence and malignancy, and often some assessment of the probable degree of malignancy, can be made for the majority of tumours. Recalling always that these terms are relative, the distinction depends on the points indicated in the tribular summary. The features outlined in this table must be briefly amplified.

(1) Structure

Tumours of a given cell type vary greatly in the degree of differentiation attained, in some this is a complete as in the corresponding normal tissue, in others annylasia or lack of differentiation of different degrees is seen

Most innocent tumours attuin a high degree of structural differentiation so that their tissues closely resemble their normal counterparts. A papilloma of the skin consists of overgrown epidermis which is structurally normal except for exagerated papillation and cornification, a papilloma of the bladder is clothed by a uniform layer of the non-cornifying stratified epithelium characteristic of the utinary tract, and a papilloma of the large intestine consists of unmistakable colonic mucosa. So also a lipoma consists of structurally typical adipose tissue, a leiomyoma of unmistakable plain muscle fibres, a chondroma of cartilage.

Malignant tumours on the other hand frequently show imperfect differentiation of varying degrees. Thus many carenomas while showing unmistakable epithelial characters, lack those details of cellular differentiation and arringement which enable us to distinguish one particular kind of normal epithelium from another, so that the histological structure alone may not enable us to distinguish extenionas of the breast stomach or prostate from one another. Other carenomas more actively growing and cellular, may even lack all recognizable epithelial characters and may be microscopically indistinguishable from highly anaplastic sarcomas ghomas or growths of other kinds. In general the degree of malignancy of tumours is roughly proportional to the degree to which they fail to attain histological differentiation, the most anaplastic tumours are the most miliciant

| _ | | | Innocent tumour | Malignant tumour |
|----|------------------------------------|---------------------|--|---|
| I | Structure | - 1 | Structure often typical of the | Structure often atvpm il 10 |
| | Mode of growth | - | particular tissue of origin Growth usually purely expansive and a capsule formed | differentiation imperior to growth infiltrative as well as expansive to that that encapsulation is absent |
| 3 | Rate of growth - | - ! | Growth usually slow mutotic figures scanty | Growth may be rapid with many |
| 4 | End of prowth - | - | May come to a standstall or retrogress | progres we to a fatal termina |
| 6 | Metastasis - Clinical results - | | Absent Dangerous only becau e of (a) position or (b) accidental complications | frequently present Intrastically dangerous because of propressive infiltrative growth and metastasis |
| (* | Faotnote) | William manufalliam | (c) production of excess of hormone | \$10424 Aug 116(192, 43)\$ |

Attempts at precise histological grading of malignant tumours as an index to their degrees of malignancy are very arbitrary and unscientific. Broders is method of grading which has been widely adopted consists in daviding malignant growths of any given class into four groups according to whether one two, three or four quarters of the cells appear incompletely differentiated. In view of the great variety of cellular structure to be seen in different immembers of most classes of tumours and often in a single tumour, the application of Broders is method seems to me to be largely guesswork. Tumours show great eviological variation and the decision as to which cells shall be libelled "differentiated or undifferentiated", as the case may be greatly depends on the personal bins and preconceptions of the examiner. It is not surprising to learn that different graders reach different conclusions on the same material. All competent pathologists grade, tumours to the extent of forming and expressing opinions as to their probable degrees of malignancy from their general invological structure and broad groupings of tumours according to their degree of maplanaria like those of

[°] C. W. Authorium statisty suggested the following: I stand a state of peak by district end broad a function of the state of the base of the state of the stat

INNOCENCE AND MALIGNANCY

reenough or Healy, are of value Broders s and other similar grading methods we no greater precision by using numbered labels, attached in accordance the certain arbitrarily chosen and highly variable histological characters

It must be pointed out also that the numerical correlations between grading in prognosis advanced by graders in support of their systems are of no real f. Such correlations are bound to appear with any system of grading hatever which does not quite ignore the simple generalization of broad paralbetween the degree of anaplasia and the degree of maligniney of tumours any given group. For individual prognosis, no scheme of grading can attining accuracy than the general principle affords. It is to be hoped that the bad

raccuracy than the general principle affords. It is to be hoped that the bad but of recording such diagnoses as 'squamous cell carcinoma grade 2, "adeno unoma grade 3, will soon cease to be a fashion

To the important general rule that being tumours are typical and malignant umours atypical in structure, there are notable exceptions to which reference already been made. Tumours of the thyroid afford good examples in both irretions on the one hand, some of the being adenomis of the thyroid contain. It imperfectly formed vesicles devoid of colloid, or even diffusely cellular races, on the other hand, some of the adventure of the thyroid contain.

imperfectly formed vesicles devoid of colloid, or even diffusely ceitiliar reas, on the other hand some of the adenocarcinomas of the thyroid contain treas of typical colloid filled vesicles indistinguishable from normal thyroid usual We have already referred to and rejected the notion that innocent tumours metastasize but the very invention of such phrases as "metastasize but the very invention of such phrases as "metastasize but the very invention of such phrases as "metastasize but the very invention of such phrases as "metastasize but the very invention of such phrases as "metastasizing gottre".

metastasize out the very invention of such parases as "metastasizing goitte", metastasizing chondroma "" metastasizing myoma", etc. serves to stress the that malignant tumours do not always show an atypical structure. As Nichol on pointed out, a squamous celled careinoma of the skin may attain such a high degree of differentiation that it might well be spoken of as malignant skin. So also some of the visceral careinomas differentiate so well, in parts at least, that histological identification of the particular region of origin, such as kidney, prostate or bowel is possible. As Foulds says, it is evident that an elaborate organization of structure and function is consistent with malignancy.

(2) Mode of growth

Many innocent tumours are strictly localized growing purely by expansion, so that if surrounded by other tissues, these are thrust aside and compressed, and the tumour is often distinctly encapsulated. This applies to adenomas myomas lipomas, and many other beniga tumours. However, not all benign tumours are sharply circumscribed. Osteoclastomas show no capsule nor microscopically sharp delimitation from adjacent bony tissue and marrow, and while many fibromas and meningiomas are well encumscribed some members of these species show limited infiltration of neighbouring tissues. Angiomas also are never encapsulated or sharply delimited their vessels merging into the normal ones with which they communicate and mingling with adjacent normal tissues, but most angiomas are malformations and not true tumours.

Besides growing by expansion malignant tumours also grow by infiltration ie the tumour cells penetrate into the interstices of the surrounding tissues and grow along tissue spaces lymphatics or blood-vessels. Even when malignant tumours appear to the naked eye to be sharply circumscribed microscopical examination of the margins often reveals that the tumour cells are infiltrating

the neighbouring tissues. Inconspicuous infiltration may be present for long distances beyond the macroscopically visible edge of the growth. It is this marginal zone of infiltration which makes malignant growths so prone to recur after surgical removal unless a wide excision of the surrounding tissues is carried out.

(3) Rate of growth

Most innocent tumours grow only slowly and show few mitotic figures in the tumour cells. Many malienant tumours, on the other hand, grow rapidly, and mitotic figures are readily found in the cells. Anaplastic tumours contain many mitotic figures, and the mitotic activity of a tumour is prohably the most reliable single criterion of its degree of malignancy. If in doubt regarding the malignancy or otherwise of a particular tumour, search for mitotic figures in the tumour cells, if several of these are found easily, then the tumour is almost certainly a malignant one However, not all malignant tumours grow rapidly, many of the well differentiated adenocarcinomas scirrhous cartinoma simplex. some of the fibrosarcomas, grow slowly and contain relatively few mitotic figures. On the other hand the slowly growing basal-cell careinomas of the skin often contain many mitotic figures-a remarkable exception to the parallelism between the numbers of mitoses and the degree of maligniney of neoplasms The duration of mitosis in various tumours is worthy of study, perhaps in the basal celled growths mulotic figures are numerous, not because of rapid cell division but because of retardation or arrest of the later phases of mitosis just as happens from the action of colchicine. Mitosis in tumours is described more fully in Chapter 8

(4) End of growth

While most true neoplasms benign or malignant, grow continuously and indefinitely spontaneous cessation of growth and retrogressive changes are seen much more frequently in benign than in malignant tumours. This is not infrequent in adunomas of the thyroid or breast, in uterme myomas and in liponias fibromas and meningiomas. Retrogressive changes, namely fibrosis, eystie change and calcification, are most familiar in adenomas of the thyroid and myomas of the utrus. At necropsy, small meningiomas heavily calcified and clearly quiescent, are sometimes found. Benign teratomas especially the so called dermoid cysts of the ovary, may be seen in a state of sentity and quiescence, either when discovered incidentially at operation or necropsy or when surgically removed because of some accidental complication.

M dignant tumours on the other hand, very rarely cease growing spontaneously but proliterate and extend continuously to a fatal ending There do occur nowever, very rare cases of spontaneous disappearance of proven malignant growths including mammary careinoma papilliferous ovarian growths with peritoneal metastries malignant melanoma, and other tumours Useful reviews of this subject are those of Gaylord and Clows (1906) Rohdenburg (1918), Strauss (1927) Frauchiger (1929) Willis (1934), and Ewing (1940)

Complete permanent spontaneous disappearance of a mahanant growth is extremely rare if indeed it ever occurs but this does not detract from the great interest of partial and temporary retrogressions. The factors responsible for

'ese phenomena are unknown, but the fact that retrogression has overtaken with widespread metastrises shows elerify that these factors are systemic 4 metabolic rather than local In this connexion we may recall the acceleration of growth which has often been observed in mammary carcinoma during pregnancy and lactation, and the retardation and even quiescence of the growth after weaning This phenomenon shows that the growth of a malignant tumour is not entirely independent of the general condition of the organism. Its tissues not only draw their nutrition from the body politic, but are affected adversely or otherwise by its metabolic state. It is then not inconceivable that a fumour which is successfully progressing in its nutritive competition with the healthy tissues, and which unhindered will eventually destroy life, may have the balance turned against it by some sudden metabolic alteration of the organism and it may not be insignificant that cases of spontaneous retrogression of malignant tumours have often given a history of preceding surgical operation or febrile illness. A tumour is not, as we often tacitly assume something foreign to the body, possessing unlimited independent growth capacity but rather a part of the individual's own tissues subject like them to the metabolic state of the body and to the largely unknown laws of senescence and death. This conception, though rather nebulous. provides at least a plausible view of the curious fluctuations delays, recrudescences and retrogressions observed in the life history of some neoplasms

(5) Metastasis

As has already been remarked, the development of discrete secondary growths in other parts of the body is proof of the malignant nature of a tumour, no matter how slow its growth or how innocent' its histological structure. Metastasis depends on the infiltrative invasion of lymphatics blood vessels or scrous and other cavities, and the detachment and transfer of tumour particles. These phenomena will be described in Chapters 9 and 10

Not all milignant tumours produce metasiases Thus rodent erreinomas are acknowledged malignant tumours in that they are locally invisive and destructive yet they rirely or never metastasize. The same applies to the so called "adamantinomas", these also invade and destroy the bones and neighbouring tissues and always recur unless wide exersion is undertaken, but they do not produce metastases. So also most of the gliomata are infiltrating and destructive tumours, and the more rapidly growing of them are highly cellular and speedily fatal, yet, apart from occasional dissemination in the cerebrospinal spaces these tumours never metastasize. In most classes of tumours which frequently produce metastases there occur members which fail to metastasize even after a long period of active growth and the attainment of a great size

(6) Clinical results

Benign tumours may prove harmful in any of three ways, (a) by virtue of their position (b) as a result of secondary complications or (e) in the case of endocrine tumours by the production of excess of hormones The following examples are illustrative

(a) Position

An intracranial tumour e.g. a meningioma auditory nerve tumour or pituitary adenoma no matter how well circumscribed or how slow in growth it may be, is always clinically serious because of its position. A progressively enlarging tumour in the anterior mediastinum e.g. a retrosternal thyroid adenoma or a cystic teratoma will eventually compress the trackea or the great vissels. A benign myoma of the uterus or a benign ovarian tumour during pregnancy may become incarcerated in the pelvis, leading to serious compression of pelvic viscera or to dystocia.

(b) Accidental complications

Haemorrhages take place from beingn tumours of mucous membranes, e.g. papillomas of the urmary or alimentary tracts, or from submucous tumours which distend or perforate these membranes, e.g. uterine myomas. The same tumours may suffer surface ulceration and infection and infection is particularly serious if it involves a bulky tumour, e.g. a large uterine myoma or a huge mammary fibro adenoma which has distended and perforated the skin. A pedunculated tumour such as a subserious myoma, or an ovarian cystadenoma or teratoma may suffer strangulation by torsion of its pedicle, and a pedunculated tumour in the intestine is lirible to initiate an intussusception.

(c) Production of excess of a hormone

This is exemplified by the aeromegaly or grantism resulting from an eosinophil adenoma of the pituitary gland by generalized fibrocystic disease of the skeleton aecompanying parathyroid adenoma or by the hypoglycaemic attacks observed with insulin secreting adenomas of the pancreas

Malignant tumours may produce illness in the same three ways, and indeed the dangers of position and accidental complicitions are much greater with malignant tumours because of their more rapid growth and their inhitrative and destructive properties. In addition, these properties and the related propensity for metastasis give malignant tumours intrinsically dangerous characters not shared by benign tumours. Because of its progressive growth invasive nature and metastasis. I malignant tumour cannot grow for long in the body without reaching and seriously affecting some important organ of suffering some serious complication. The question whether malignant tumours bring about eacheval in any specific chemical way warrants discussion in a separate section.

THE CACHEXIA OF MALIGNANT DISEASE

It has been a prevalent idea that "malignant cachevia" is a peculiar specific result of the growth of a malignant neoplasm in the body, attributable to hypo thetical poisons elaborated by the growth or to its parasitic utilization of food substances to the detriment of the normal tissues. I have known students to derive from their clinical teaching the impression that malignant cachevia was an almost necessary accompaniment of malignant disease, and that its absence in a case of obscure nature was of diagnostic value in helpingto exclude malignancy. I have heird a reputable clinician say that he could often spot' a case of malignancy by the characteristic middly complexion." Such views must be rejected, because (1) no toxic products of timiour growth capable of causing cachevia have been identified (2) the nutritive requirements of timiours is rarely so great as to be a significant contributing factor in undermining health and (3) the presence or absence of cachevia in cases of malignant disease is clearly referable

to the presence or absence of obvious enough harmful effects of the growths on bodily functions. These points require amplification

(1) The possible formation of toxic substances by tumours

As will be discussed in Chapter 8, much work has been done on the metabolism of tumour tissue, but no peculiar metabolites have been identified that some rapidly growing tumours produce large amounts of lactic acid, but this substance is readily converted by the liver into glycogen and there is not the slightest reason to think that it contributes to cancerous cachexia. In any case the majority of tumours of slow or moderate rates of growth do not produce unusual amounts of lactic acid

In cases of advanced cachexia, chemical alterations of great variety and degree have been observed alterations of blood sugar of liver glycogen, of nitrogen metabolism of mineral balance of the blood picture of alkali reserve, and the But these are all clearly the results or components presence of acetone hodies of cachevia and not its primary causes similar changes are seen in advanced debility from other causes such as starvation chronic gastro intestinal disease or tuberculosis No chemical changes peculiar to malignancy have been observed ın malıgnant cachevin

Another possibility to be considered is that, from bulky degenerating tumours, soluble products of degeneration might be absorbed into the circulation and might have toxic effects. This possibility must be admitted, but unless bacterial infection supervenes in degenerating growths, there is no positive evidence that the products of degeneration have serious toxic effects. The soluble products of autolysis of tissues are mainly amino acids, uric acid, creatine, creatinine, glycerin fatty acids and morganic salts—in fact, the usual split products of proteins. fats and the other constituents of protoplasm, all of which the body is well accustomed to metabolizing and which could not function as toxic agents. Moreover, many cachexia producing tumours are neither bulky nor degenerated so that they cannot be a source of autolytic products in any appreciable quantities

(2) Nutritional demands of tumours

Do tumours harm the rest of the body by stealing food from it? This view, which has been strongly held by some writers has only to be studied a moment to be seen to be baseless. A tumour which like a foetus increases its total weight by a pound a month is an exceptionally rapidly growing tumour yet it cannot be contended that increase of a superfluous tissue even at this rate would place an insupportable burden on the alimentary and metabolic functions of the body On an adequate dict the nutritional state of a pregnant woman does not suffer as a consequence of the rapid growth of 10 pounds or more of foetal tissue. Most tumours, however have rates of growth much lower than this indeed with many fatal malignant growths, the total mass of tumour tissue in the body at the time of death amounts to only a few ounces Clearly the nutritive demands of such growths can be but trifling and an altogether negligible factor in causing the cachexia which they brought about

It may be suggested that it is not the mere bulk in growth of a tumour that matters but that tumours may have special nutritive requirements and may deprive the body of unduly large amounts of such essential factors as vitamins special amino acids or the scanter immeral constituents of our diet. This, however, is pure speculation and as we shall see later study of the chemical composition and metabolism of tumours affords no evidence that they have any peculiar nutritive requirements.

(3) Factors contributing to eachevia

Cancerous cachevia is indeed readily accounted for without postulating unidentified toxins or extrivagant nutritive demands. It is the result not of any peculiar properties of malignant neoplasia per se but of such obviously debilitating factors as starvation, haemorrhage ulceration bacterial infection destruction of functionally vital tissues pain sleeplessness and anxiety

Consider for example the extreme eachexia of many cases of cancer of the stomach. In large part this is the cachexia of starvation resulting from poor appetite diminished peptic digestion impaired gastric mothlity pyloric obstruction or all of these. Haemorrhage ulceration and pain also contribute to the result. In some cases extensive metastases in the liver impair hepatic function and so place an extra burden on nutrition and metabolism, jaundice may be added. In other cases pertoneal dissemination leads to recurrent ascites with corresponding loss of proteins and to impaired bowel mothlity. Metastases in the upper abdominal lymph glands may extend to obliterate the esterna chyli and thoracic duct doubtless impeding the absorption of digested fats. Sometimes even chylous ascites may result. Anaemia may result no only from the general impairment of nutrition but also occasionally in more specific ways sometimes through the destruction of the gastric tissue reducing the haemopoietic factor sometimes by widespread metastatic destruction of red bone marrow.

Similar sequences are apparent when cachexia accompanies carcinoma of the ocsophagus or of the intestines or indeed any other kind of maligninal desease Carcinomas of the tongue tonsil or pharyax produce cachexia mainly disease ton haemorrhage infection pain and diminished food intake through dysphagin carcinoma of the uterus by haemorrhage ulceration urinary obstruction and infection and uraemia carcinoma of the breast by local ulceration and infection or more often by the pain and destruction wrought by metastatic growths in liver bones lungs brain and elsewhere and so on All observant clinicians and pathologists are well aware that the subjects of malignant discuse who have been spared such results as those described above do not exhibit cachexia. This is frequently the case with carcinoma of the breast which even in an advanced state with widespread secondary growths may be accompanied by little or no emaciation or anaemia. On the other hand, how great is the cachexia of advanced pulmonary tuberculosis or of an unreflexed eltronic pytlore ulcer!

There is indeed no such thing as a specifically malignant cachexia Cachexia means merely debility malinutration anaemia emaciation from any causes and malignant tumours are one of the most common and least remediable of these causes

CONCLUSION

Innocence and malignancy are not two distinct biological properties pertaining to neoplasms but merely convenient terms which have become firmly

entrenehed in pathology because of their prognostic value. By experience of each histogenetic class of timours, we have learnt which particular timours in that class are likely to remain local in their growth and to be curable by local removal and which ones will spread more or less widely and dangerously. The pathologist knows, however, that in most classes of timours growths of intermediate behaviour occur, for the prognosis of which the bald terms 'innocent' and malignant must be qualified. Between the cellular characters of timours and their degrees of malignancy there is a broad parallelism, largely based on the inverse relationship of rate of proliferation and degree of differentiation of timour cells. To this parallelism however, there are many exceptions

The notion that to neoplisia is false So also is the notion that there is a specific "malignant' cachexia

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CHAPTER 4

THE EXPERIMENTAL PRODUCTION OF THMOURS

DURING the last three decades our knowledge of the causation of tumours has advanced rapidly Studies of two kinds have contributed to this advance (a) authorized studies of occupational social and ricial factors in the causition of human neoplasms, and (b) studies in the experimental production of tumours in animals by means of chemical and other agents. These two kinds of researches have stimulated each other. The recognition of occupational and other factors in the genesis of certain kinds of human tumours often preceded and indeed gave birth to the successful production of their experimental counterparts.

Now however, much of the knowledge gained experimentally has become so precise and so far in advance of that deducible from studies of human material. that the general discussion of causation is best commenced with an outline of the experimental achievements

In the following account only a small fraction of the now enormous volume of published work can be reviewed. For further details and references the reader should consult the papers of Barry et al. (1935). Cook et al. (1936). Kennaway and Kennaway (1937). Cook and Kennaway (1938 and 1940). Badger et al. (1940). and 1942) Willis (1945), and the monograph by Hueper (1942) Staemmler's and Bauer's reviews of occupational tumours (1937) are also useful

SECTION 1

THE CARCINOGENIC HYDROCARBONS

(1) Skin cancers in man due to tars, oils and allied substances

Long before the isolation of earcinogenic hydrocarbons in a pure state an achievement only of the last two decades it had been recognized that those whose occupations exposed them to soot tar pitch mineral oils or creosote were prone to develop cancers of the skin lt was in 1775 that Percival Pott described chimney sweep's cancer of the scrotum the first clearly recognized occupational eneer A century later Volkmann described the first recorded cases of paraffin carcenoms of the skin and increasing numbers of trand oil cancers were reported thereafter. The most useful of the earlier reviews of the subject is that of Ross (1918) and the Report of the International Conference on Cancer (London 1928) Brockbank's monograph on cotton spunier's cancer (1941) and Hueper's book on occupational tumours (1942) contain much viliable information on the historical and technological as well as the clinical and expers mental aspects of the subject

(2) Experimental far and oil cancer

knowledge of decupational tar and oil cancers naturally led to attempts to produce tumours experimentally by using similar means. As long ago as 1889
Hinau painted rate with tir and similar substances but produced only chronic dermitus. If only he had chanced to use mice instead of rats he might have forestalled the first successful experimental production of cancer by a quarter of a century. In 1894 Cazin also was unlucky in choosing another resistant species, the dog, five months tarring evoked no tumours. In 1912 Bayon all but achieved success, he observed epithelial overgrowth, but without invasion after the injection of gas tar into the ear of the rabbit, the soil and the agent were suitable, but the duration of the experiment was insufficient.

It was the good fortune of two Japanese workers, Yamagiwa and Ichikawa, to apply a suitable agent to a susceptible animal for a sufficiently long time. In 1914 and 1915 they reported the development of papillomas and carcinomas in the skin of rabbits ears following long continued application of the The First World War, however delayed recognition of this achievement, and it was not until 1918, when they again reported their results, that world wide interest was aroused and modern experimental erreinogenesis was fairly launched. The earcinogenic properties of oils were first proved experimentally by Leitch in 1922.

Experimental tar and oil cancer has been the subject of an enormous volume of research admirably summarized by Woglom in 1926 and by Seelig and Cooper in 1933. Only the barest outline of the main results can be given here. It was soon found by many workers that, of the common laboratory animals, only the rabbit and the mouse were highly susceptible to the development of tar cancer of the skin, rats guinea pigs, dogs and fowls were found to be almost completely share this resistance was shown by the development of tar sarcomas following repeated subcutaneous injections in rats and in fowls, results which more recent experiments with pure carcinogenic hydrocarbons have confirmed

When a potent tar or oil is applied twice or thrice weekly to the mouse s or rabbit s skin, papillomas often referred to as tar warts" and often multiple, develop in from 30 to 100 days or longer and earcinoma in from 50 to 500 days or longer. Few carcinomas appear in less than 100 days. For the mouse the times of appearance of papillomas are nearly the same as for the rabbit, but malignant change takes place much more readily in the mouse. For this reason and others, mice have been used much more than rabbits in experiments on carcinogenesis. Carcinomas usually develop from tissue which is already papillo matous, and are of the ordinary cornifying epidermoid type. While most animals will have developed tumours by the eighth or ninth month, a few tardy tumours will appear later than this and a small proportion of the animals may full to produce tumours in spite of prolonged tarring.

The duration of tarring is important. Most mice painted for four months eventually develop tumours a less proportion of those painted for three or two months do so and the tumours appear on the average later than in animals painted for longer periods while many animals painted for only a month or less fail to develop tumours later. The important phenomenon of a long latent period between the cessation of tarring and the appearance of tumours, often many weeks or months in mice was particularly stressed by Leitch

Attempts have been made to shorten the latent period and increase the tumour yield by modifying the painted area by trauma, heat or other agents Deelman (1924) and others found that wounds of a tarred area localized and hastened tumour formation and this 'Deelman phenomenon' has been confirmed using pure carcinogenic hydrocarbons (Pullinger, 1943 and 1945) Cramer (1929) found that injury to an already established benuen tar wirt is apt to precipitate

malignant change. Orr (1934) found that subcutaneous injuries by linen sutures or adrenaline injections hastened the development of tar tumours in the overlying epidermis a result confirmed later (1935) using dibenzanthracene entity does not increase the susceptibility of skin to tar cancer indeed some workers have noted diminished susceptibility. Twort and Twort (1936) found that previous applications of oleic acid increased the caterinogenic potency of tar, while lactic acid lanolin and some other substances diminished it

Many workers have observed that different sites show different degrees of susceptibility to the carcinogenic action of tar and oils (e.g. Orr, 1935). The interscapility area of mice is more sensitive to tar than the sacral or abdominal skin while the soles of the feet are the most resistant. Animals which are sensitive in one area are usually relatively sensitive in another area (Twort and Twort, 1936).

It remains only to add here that in addition to epidermal papillomas and carcinomas certain other kinds of tumours have been produced by tar. Reference has already been made to sarcomas following subcutaneous injections of far in rats and fowls as well as in rabbits and mice. But, even surface applications may occasionally induce sarcomatous change in the dermis (Deelman 1922), Leitch 1922). Melanomas following tar applications have been described in mice by Lipschutz (cited by Woglom) and in dogs after very prolonged tarring by Prissey (1938). The phenomenon of increased meidence of tumours of remote sites following skin tarring will be discussed later.

(3) The search for the carcinogenie agents in tars and oils

Since tars and oils are highly complex mixtures of substances and since different tars and oils were found to vary markedly in their carcinogenic efficacy, it soon became evident that a search must be made for specific ingredients responsible for earcinggenesis. Many workers (cited by Worlom) investigated the relative efficacy of tars of different kinds of different tar fractions obtained by distillation and of tar extracts made with solvents. Notable amongst these was J. A. Murray (1922) who prepared a highly careinogenic ethereal extract of tar. But by far the most important of the researches into the chemistry of carcinogenic tars were those of kennaway and his collaborators from 1923 onwards the main results of which were outlined by Kennaway in 1930 These showed that the earcmogenic factor in tar was present in the higher boiling fractions that potent carcinogenic tars could be made artificially by heating acetylene, isoprene skin, yeast, cholesterol or human skin or voluntary muscle to temperatures between 700° and 920° C and that a non-carcinogenic petroleum could be made carcinogenic by heating to 800 C in the process of which aromatic hydrocarbons are formed from those of the aliphritic series. Twort and Fulton (1930) prepared highly active tars by heating turpentine and pinene

In 1930 Mayneord and Hieger working with Kennaway made the important observation that the fluorescence spectra of many cancer producing mixtures including gas tar acetylene tar yeast tar muscle tar cholesterol tar ethereal extract of gas tar pitch distillate heated petroleum and shale oil showed the same bands at wase lengths 4 000 4 180 4 400 A (Hieger). These bands were take those of the fluorescence spectrum of the polycyclic hydrocarbon 1 2 benzan thracene. Accordingly, Kennaway (1930) made a special study of hydrocarbons.

allied to 12 benzanthracene, and found 1256 dibenzanthracene to be carcinogenic. At last a chemically pure carcinogenic compound had been identified, not indeed as a constituent of tar, but as a result of painstaking studies of the

TABLE I

SOME PURE CARCINOGENIC HYDROCARRONS AND ALLIED SUBSTANCES

| 8 9 4 6 5 10 4 1 2 Benzanthracene | Dibenzanthracene | CH ₃ 9 10-Dimethyl-1 2- Bersanthracene |
|-----------------------------------|---|---|
| | CH.3 | |
| Cholanthrene | Methylcholanthrene | 3 4 Вепзругеле |
| CH ₂ Oldenziftvorene | CH N N N 1256- Dibenzacridine | NH 1 2 5 6- Dibenzcarbazole |
| | CH2COH (12) CH3 (12) CH3 (12) CH3 (12) CH3 (12) CH3 (12) CH3 (13) | |
| 3 4-Benz phenanthrene | Desoxycholic Acid | Beta anthraquinoline |

physical and chemical characters of carcinogenic tars. Kennaway was careful to point out that "neither benzanthracene nor any of its derivatives have been found and perhaps have not been sought for, in coal tar, and to suggest prophetically

that among the many compounds still undiscovered in tar some might be found far more powerfully carcinogenic than any known substinces. So also Hieger in discussing the significance of the discovery of characteristic bands in the spectra of carcinogenic mixtures insisted that the substance responsible for the bands may not be identical with the cancer producer but its some closely allied compound. The carcinogenic agent in tars and oils may be only one of a group of such compounds? The value of the fluorescence test was in Hieger's on words to indicate the probability of carcinogenic activity and to assist in directing the preparation of appropriate hydrocarbons.

(4) Pure caremogenic hydrocarbons

The importance of the discovery of pure carcinogenic hydrocirbons by the London workers can scarcely be exaggerated. It gave a tremendous impetus to both chemical and biological work in this field. Many new circinogenic compounds have been produced and tir cancer research has largely been superseded by more precise researches with these chemically pure substances. The number of such substances now runs into scores and only the most important can be mentioned here. (See Table I.) For more detailed accounts consult the papers of Kennawiy and his co-workers already cited, and those of Fieser (1938) and Shear (1938).

(a) Simple derivatives of 12 benzanthracene

This substance 1.2 benzanthracene itself is only very feebly externogenic but many of its simple substitution derivatives are much more active. This applies particularly to derivatives containing substitution groups at the positions 10.5 9 and 6 of the benzanthracene complex. Thus 10 methyl 1.2 benzanthracene. 9 methyl 1.2 benzanthracene. 9 methyl 1.2 benzanthracene and 6 methyl 1.2 benzanthracene benzanthracene in the order of decreasing potency. Further if suitable simple substituents are introduced into 100 of these favourable positions they then reinforce each other, giving a highly potent carcinogenic compound. This applies to the 5.6.5.9.5.10 and 9.10 dimethyl derivatives. The list named is the most active eatemogenic hydrocarbon so far discovered and co-workers obtained skin cancers in mice as early as the 32nd day after the initial application.

(b) Methylcholanthrene and cholanthrene

These ment special interest not only because the former is second only to 9 I-dimethyl 1.2 benzanthracene in carcinogenic activity but also because the 10-dimethrenes are closely reluted chemically to the bile acids. Thus methyl-cholanthrene has been prepared from both desoxycholic veid and cholic read and both it and the parent hydrocarbon cholanthrene has also been synthesized Ethylcholanthrene has also been prepared and shown to be an active carcinogen From the structural formulae (Table 1) it will be seen that these compounds again are reilly 1.2 benzanthracene derivatives with substituents in the carcinogenenically favourable positions 10.5 and 6. methylcholanthrene being particularly notable in that all three of these positions carry substituents.

(c) 3 4 benzpyrene

This is certainly the most active, and perhaps the only important, carcinogenic constituent of coal tar. It was first isolated from coal tar pitch and later prepared synthetically. In accord with Kennaway is 1924 work, the highest boiling fractions of tar contain relatively large amounts of benzpyrene, and the fluorescence spectrum of benzpyrene is of the same type as that of 12-benzanthracene. Its close relationship to this substance is evident from its structural formula, which shows that it is really a benzanthracene derivative with an additional benzenering affecting position 9 where we have already seen substitution is favourable for the development of carcinogenic properties. Benzpyrene is only slightly inferior to methylcholanthrene in potency. Some of its simpler derivatives are also carcinogenic, though less powerfully so than the parent hydrocarbon (Sheir, 1939). A high order of carcinogenic activity is shown also by three hexacyclic dibenziveness which have been prepared (Cook and Kennaway, 1938).

(d) 1 2 5 6 dibenzanthracene

This is notable as being the first pure hydrocarbon to be shown to be careinogenic and since the discovery of this substance, it has been widely used by research workers. It is capable of producing tumours in a high proportion of mice, but it does so relatively slowly. In molecular structure it also is a 12 benzanthracene derivative with an added benzene ring as a substituent at positions 5 and 6.

(e) Some other carcinogenic hydrocarbons and related compounds

Certain other hydrocarbons and certain heterocyclic nitrogen containing compounds with structures analogous to the carcinogenic hydrocarbons of benzanthracene type have also been shown to be feebly carcinogenic. These include 1256 dibenzfluorene, 1256 dibenzaeridine 3456 dibenzaeridine, 1256 dibenzcarbazole and 3456 dibenzcarbazole. The ways in which these compounds resemble and differ from the benzanthracene derivatives in molecular structure are shown in Table I Dibenzearbazole also produces liver tumours in painted or injected mice (see later) It is of interest to find that 3 4 benzphenanthrene and 2 methyl 3.4 benzphenanthrene which are unrelated to benzanthracene, have considerable carcinogenic potency Morton et al (1936) also claimed that triphenylbenzene and tetraphenylmethane were carcinogenic but Cook and Kennaway (1938). Shear (1938) and others have been unable to confirm this The discovery of Kennaway and co workers, referred to by Badger et al that under certain conditions desoxycholic acid, a normal component of bile, can induce sarcomas in mice, is a remarkable one and may prove of far reaching importance

(5) The relative potency of the caremogenic hydrocarbons

The relative potency of the various hydrocarbons has been specially studied by Fieser and co authors (1937), Fieser (1938) Iball (1939) and Twort and Twort (1939) Iball after pointing out the difficulties of making accurate comparisons reviewed the results of the London workers as regards the percentage of skin tumours produced and the average period of induction for the various compounds By dividing the percentage number of tumours by the average induction period in days and multiplying by 100 to give whole numbers, he obtained an index

of potency for each compound Heading the list was 9 10 dimethyl 1 2 benzan thracene with an index of 151, methylcholanthrene followed with an index of 80, and then benzpyrene with an index of 75. The index for 1 2 5 6-dibenzan thracene was 26, while near the bottom was dibenzaendine with an index of 7 Twort and Twort using a rather different method, reached very similar conclusions as regards methylcholanthrene benzpyrene and dibenzanthracene the relative potencies of which they found to be roughly in the ratios 10 51. The results of the American workers were in general agreement with these

The solvent used influences the careinogenic properties of the hydrocarbons when applied to the skin. Benzene has been the most frequent solvent, but Crabtree (1940) found the rate of induction of tumours by benzpyrene to be much faster when ether plus 2 per cent liquid paraffin was used instead of benzene while acetone plus 2 per cent liquid paraffin was found to be much superior to benzene as a solvent for dibenzanthracene. Bradbury and co workers also found acetone a favourable solvent. Twort and Twort found the relative potencies of dibenzanthracene when dissolved in chloroform a lowly carcinogenic mineral oil oleic acid and liquid paraffin to be 60 26 22 and 3.5 respectively. The importance of the solvent doubtless has a bearing on the relative carcinogenic activities of different tars and other crude mixtures. Shear (1938) has pointed out that ribbits, though susceptible to the action of tar are more refractory to pure carcinogenic hydrocarbons than rats or nuce. and that there is experimental evidence of the presence of a reinforcing co-carcinogen. In certain tar fractions which are themselves not carcinogenic.

(6) The production of sarcomas by caremogenic hydrocarbons

In the story of tar cancer reference was made to the development of sarcomas following subcutaneous injection of tar and also following the painting of the skin The discovery of highly potent pure carcinogenie compounds greatly facilitated the experimental production of sarcomas. The first contribution in this field was that of Burrows Hieger and Kennaway (1932) who by subcutaneous injections of 1 2 5 6-dibenzanthracene in lard, obtained transplantable spindle-celled sarcomas in mice and rats. In 1933 Peacock reported similar results in fowls. Further experiments by the London workers were described by Barry and Cook (1934). and in 1935 Boyland and Burrows reported a series of 36 spindle-celled sarcomas obtained in rats and mice by repeated subcutaneous or intraperitoncal injections of colloidal aqueous solutions of dibenzanthracene. Another large series of subcutaneous sarcomas produced by dibenzanthracene was reported by Haugensen and Krchbiel (1936) who described the histological structure of the tumours in some detail. Of 49 sarcomas, they classified 11 as fibrosarcomas, 6 as leiomyo sarcomas 10 as rhabdomy osarcomas (though cross strictions were not found and the authors admit that this designation is uncertain) while 22 tumours of poorly differentiated types remained unclassified. Hangensen and Kruhbiel also described a liposarcoma produced by benzpyrene Mayneord and Parsons (1937) found that \(\lambda \) irradiation of mice either previous to or during a series of injections of a soluble derivative of 1256 dibenzanthracene accelerated tumour formation and increased the number of sarcomas obtained

The researches of Shear (1936 and 1938) were of special interest. He obtained sarcomas in mice following the introduction into the subcutaneous tissues of

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measured amounts of dibenzanthracene in cholesterol pellets, and found that amounts as small as 0 0004 milligram might be followed by the development of transplantable sarcoma This is the smallest effective dose of a carcinogen so far recorded, and it serves to show how difficult it might be to isolate and identify naturally occurring carcinogenic substances in tissues. Using pure methyl cholanthrene crystals. Shear also found that, prior to the development of tumours, the thickened tissue at the site of injection gave rise to tumours when transplanted to another animal. Transplants about 7 weeks after injection gave rise to tumours as did also a slightly enlarged adjacent lymph gland. These results were not due merely to the transfer of the hydrocarbon in the transplant, because transplants taken at an earlier stage gave negative results. In injected mice not used for trans plant experiments, tumours were apparent as early as the 58th day and there were some tumours in all of five different batches of animals by the 75th day It was clear therefore that methylcholanthrene was a very potent and speedy sarcoma producing agent Cholanthrene produced sarcomas about as quickly. but crystalline benzpyrene was a little slower In his 1938 study Shear described the production of subcutaneous sarcomas by various methyl derivatives of 12benzanthracene the most potent compounds being the 10 methyl, 5 10 dimethyl and 5.9 dimethyl derivatives. Shear also described experimental evidence that mechanical trauma did not promote sarcoma production by methylcholanthrene

Boyland and Warren performed a series of experiments which showed that different strains of mice varied in their susceptibility to the sarcoma-producing

effect of methylcholanthrene

Orr (1939) made a careful study of the sequence of histological changes leading to sarcoma in the subcutaneous tissues of mice after the introduction of paraffin pellets containing various carcinogenic hydrocarbons. These substances appeared to prevent the occurrence of an adequate fibrous reaction around the pellet, and Orr s results suggest that the development of sarcoma is closely related to this frustrated encapsulation of the foreign body Peacock and Beck found that sarcoma following injections of benzpyrene developed not in immediate contiguity with the carcinogen, but in the tissues a few millimetres away

Bonser and Orr (1939) described 160 tumours induced in mice by the subcutaneous administration of carcinogenic hydrocarbons. Sarcomas, which comprised 65 per cent of the tumours in females and 96 per cent in males, were spindle celled and pleomorphic celled growths with much variety of structure. sometimes recalling leiomyosarcoma and sometimes very vascular and possibly Giant celled tumours were common, resembling those angiosarcomatous designated rhabdomyosarcoma' by Haagensen and Krehbiel but Bonser and Orr saw no evidence that their tumours had arisen from muscle fibres considerable interest was the development in 23 female mice of adenocarcinomas. usually along with sarcoma as well The origin of these adenocarcinomas was almost certainly from mammary tissue near the site of the injection, a result confirmed in some later experiments. Some squamous celled carcinomas also appeared arising probably from epidermis or from squamous epithelium developed in relation to the injection masses or by metaplasia of other tumours tumours were designated carcino sarcomas because they appeared to consist of two independent components ic spindle celled sarcoma combined with either adenocarcinoma or squamous celled carcinoma

Not only soft tissue sarcoma, but also sarcoma of bone has been induced by carcinogenic hydrocarbons Brunschwig and Bissell saw an osteosarcoma of a mouse 5 tiba 8² months after an intramedullary injection of benzpyren

Following tar applications or the administration of careimogenic hydrocarbons by various routes several workers have observed the development of leukaemia or leukaemiod states or of lymphomas or lymphosarcomas or, in strains of numals subject to spontaneous lymphoid tumours an increased incidence and earlier development of these growths (Furth and Furth 1938 Brues and Marble 1939 Mider and Morton 1939 Law, 1941)

The production of sarcomas by the same carcinogenic agents which cooke tumours in epithelial tissues is of great interest as regards the nature of neophisia it suggests that in spite of the great diversity in the origin structure and behaviour of tumours the neoplastic change is probably fundamentally similar in all tissues and that gains in our knowledge of the nature of this change in any one tissue will probably shed light on the entire cancer problem

(7) The production of visceral carcinomas by carcinogenic hydrocarbons

Prior to the discovery of pure careinogenic hydrocarbons sporadic attempts were made to produce experimental tar tumours of virious viscera such as the stomach gall bladder bladder vigina and uterus. Occasional apparent successes were claimed but as these were few and the interpretations often open to doubt we will not discuss them further here. (References in Woglom's review.) With the discovery of pure careinogenic compounds however, much more extensive and precise studies could be undertaken in this field. We will briefly describe the results achieved in the principal organs concerned.

(a) The lungs

In 1925 Murphy and Sturm observed that a high percentage of mice receiving tar applications to the skin developed epithelial tumours of the lungs. In various experiments 60 to 78 per cent of tarred mice developed lung tumours while no tumours were found in control mice even at more advanced ages. The tumours were small white nodulus frequently multiple and microscopically identical with the well known adenomas or adenocarcinomas first fully described by Tyzzer Later workers found that similar results followed the administration of pure circinogenic hydrocarbons either by surface application or by other routes. Furth and Furth observed increased lung tumours in mice following intrasplenic injections of benzpyrene.

A notable paper is that of Magnus (1939) who attempted to produce gratine cancer in mice by introducing 1.2.5.6-dibenzanthriene twice weekly directly into the stomach. No gastric tumours developed but tumours of the lungs appeared in 95 per cent of the animals as against 4 to 8 per cent of controls. The induced lung tumours resembled those occurring spont-ineously but three-quarters of them showed histological signs of malignancy with metastasis in two mice.

Shimkin (1939) reviewed those experiments which have shown an increased incidence of lung tumours following administration of carenogens by various in Shimkin sown experiments the routes were intratriched and intravenous. In a strain of mice with a natural incidence of lung tumours of about

20 per cent a single administration of 0.1 milligram of methylcholanthrene or of dibenzanthracene dispersed in a horse serum and cholesterol vehicle, produced multiple lung tumours in almost all treated animals surviving four months or longer After intravenous injections, nearly all mice given methylcholanthrene and about 60 per cent of those given dibenzanthracene, developed lung tumours In view of the efficacy of injected material in producing lung tumours in mice. it appears probable that the substances however applied, reach the susceptible lung tissue via the circulation after absorption in small amounts from the site of application Experiments by Lettinga (cited by Cook and Kennaway) confirm this view. Mice were given graded amounts of dibenzanthracene subcutineously. those receiving small amounts developed few lung tumours, often no more than control animals, while those given large amounts frequently developed many tumours, up to 40 or more in one animal. This result strongly suggests overflow and systemic absorption of the carcinogenic agent from the site of injection Evidently then a locally acting carcinogenic agent may also act on a susceptible tissue remote from the site of initial application of the agent, a phenomenon which may possibly be of great significance as regards some kinds of spontaneously occurring neoplasms (Experimental work on inhaled dusts and lung tumours is discussed later)

(b) The kidney

Iffield (1936) inserted cholesterol pellets containing careinogenic hydrocarbons into various viscera of nuce and rats, and obtuined his most successful results in the kidneys. All of 12 renal tumours induced in this way were of epidermoid type, suggesting an origin from the renal pelvis. Adenocarcinomis of the renal parenchyma in rats which had been given subcutaneous injections of β in thraquinoline, the structural formula of which closely resembles that of 12 benzan thracene were observed by Sempronj and Morelli (1939). Should this result be confirmed, it will illustrate a remote selective effect of the agent on renal tissue

(c) The alimentary canal

Many experiments (cited by Magnus, Peacock and Kirby, and Cook and Kennaway (1940)) in which carcinogenic hydrocarbons have been administered by ingestion, have failed to produce tumours of the stomach or intestines or the apparently successful results have been unconvincing or too few to be certainly significant. Negative results are not surprising in view of the brief duration of contact of the material with any given area of mucosa its dilution with food, and the probable protective action of mucus However Waterman, Peacock and Kirby Badger et al, and others have reported tumours of the stomach in mice after feeding with benzpyrene methylcholanthrene or other substances, and it is not unlikely that further experiments will reveal the conditions necessary in order to produce alimentary carcinomas by ingestion of carcinogenic sub stances It must be added that great caution is necessary in assessing the significance of apparently successful production of gastric tumours in rodents since vitamin deficiency can cause tumour like proliferations (Passey Beck and Peacock, Brunschwig and Rasmussen), and since some strains of animals spontaneously develop many adenomatoid lesions (Stewart and Andervont)

(d) The liver

Iffield obtained careinoma of the mouse's liver by locally introduced dibenz anthracene pellets. It is also of interest that 3 4 5 6 dibenzearbazole, applied to the skin of mice, may produce bile duct proliferation and hepatoma like tumours (Cook et al. 1936) not only because this again shows action at a distance but also because this substance is related chemically to β naphthylamine to be discussed later.

(e) The genital system

Following repeated intratesticular injections of dibenzanthracene in rabbits Lacassagne saw an adenocarcinoma probably of the epididymis in one animal Also by locally introduced carcinogenic agents. Ilfield obtained uterine carcinoma in mice and Moore and Melchionna carcinomas and sarcomas of the prostate in rats. Burrows and Boyland suggested that just as the incidence of spontaneous lung tumours in mice is increased by a carcinogenic compound given by almost any route so it is possible that the incidence of uterine adenoma and carcinoma in rabbits may be increased by either local or remote applications of carcinogenic hydrocarbons. But they were careful to point out that since uterine tumours often occur spontaneously in the rabbit, their experiments did not proce conclusively that their diberaranthracene applications had indeed played a part

(f) The breast

We have already noted Bonser's experiments (1939 and 1940) in which mammary adenocareinomas were evoked by neighbouring subcutaneous injections of earcinogens. Orr (1943) obtained many mammary carcinomas in mice of breeds which did not naturally develop such tumours by means of intransal administration of methylcholanthrene.

(g) The salwary glands

Franseen and eo workers obtained epidermoid careinomas of the salivary glands in rats and mice following the local introduction of errcinogens

(8) The production of tumours of the nervous system by carcinogenic hydrocarbons

Seligman et al (1939) described 11 gliomas and 2 fibrosarcomas which developed in the brains of muce following the introcerbral implantation of methylcholanthrene pellets. In structure the gliomas closely resembled the various types seen in human beings. One of the tumours was successfully transplanted Confirmatory results were obtained by P.ers and by Zimmerman and Arnold In some simular experiments of my own in 1934 and 1936, the introduction of pure crystalline dibenzanthracene into the brains of 30 rats failed to produce any tumours in periods ranging from 6 to 12 months. Possibly these times were insufficient for the relatively slowly acting carcinogen.

(9) Remote action of carcinogens

Experimental work shows unmistakably that carcinogenic hydrocarbons may be absorbed from their initial site of application and may then be effective in evoking tumours in other susceptible tissues. We have already noted the increased

incidence of lung tumours and of lymphoid tumours in susceptible mice, following administration of carcinogens by almost any route, and a similar increased incidence of liver tumours has been observed. In Orr's experiments already ented in which mammary carcinomas resulted from the intransal administration of methyleholanthrene, it seems clear that the carcinogen could not have contaminated the breasts in any direct way but must have reached them after absorption. Bridger et all record instances of multiple tumours of several different issues following injections or ingestion of potent hydrocarbons. Of interest in this connection are the studies of Peacock and others on the absorption, distribution and fate of polyecyle hydrocarbons in the body.

(10) Constitutional factors influencing carcinogenesis by hydrocarbons

When a carcinogenic agent is applied to a number of mice of mixed stock, there is much individual variation in the date of development of tumours and some animals may never develop tumours even after long periods. Further different inbred pure strains of mice differ in their susceptibility to enrange agents. It is possible by selective breeding to produce a race of mice specially sensitive to the action of tar and pure erreinogenic hydrocarbons on the skin (Bonser 1938). Such animals do not necessarily show increased susceptibility of other tissues, indeed Bonser later (1940) found that her skin susceptible mice were less susceptible than other strains to the induction of sarcoma by subcultaneous inactions of methyleholanthrene.

Since the incidence of mammary tumours in inbred strains of mice is known to depend partly on genetic fretors, various workers have attempted to trace a relationship between the incidence of breast tumours and the susceptibility to enronogenic agents applied to the skin of injected. Thus Cramer (1936) and others concluded that the skin of animals prone to develop mammary encer was definitely resistant to the action of enreinogens, and postulated an hereditary antagonism for enreinogeness in the two sites skin and mamma. The results of other workers (cited by Bonser) have not confirmed this view, there is great variation in the results obtained in different laboratories. It appears probable that each kind of tissue in each strain of mice has its own type of enreinogenic response, and that the susceptibilities of different tissues, such as skin and breast, are independent of one another.

(11) The mode of action of earemogenic hydrocarbons

The way in which hydrocarbons induce neoplastic change is still obscure Relevant to the problem are (a) the pre ennecrous histological changes in tissues exposed to these agents (b) the state of the tissues during the latent period which may intervene between exposure to the agent and the appearance of tumours (e) co carcinogens and anti-carcinogens (d) the effect of carcinogenic hydrocarbons on tissue cultures (e) and on lower animals or plants and (f) the chemical changes taking place in carcinogens in the tissues

(a) Histological changes in tissues exposed to carcinovenic hydrocarbons

Early observations on the pre cancerous changes in tarred skin well described by Deelman (1923) and by Woglom were difficult to interpret because non-specific irritative changes due to the crude mixtures were present. The preparation

of chemically pure hydrocarbons obvisted this and permitted study of the early pre-cancerous changes evoked by the cartinogen alone. However the work of Declimin and others on the histogenesis of far tumours provided much essential information which the later studies with pure cartinogens confirmed and amplified. The changes observed in tarried mouse skin were hyperplastic thickening and stratification of the epidermia accompanied by increased mitosis in the basal layer leading on to the development of papillary outgrowths, and later atypical growth with irregular cormification accompanied by increased mitosis in all layers going on to invasive cartinoma. Declimans work showed clearly that these proliferative changes affected a considerable area of epidermis and that the development of papilloma and careinoma in this area was demonstrably multicontrie, and multicollular.

Using methylcholanthrone and cholanthrone Page (1958) found that mouse ep dermis showed a prompt increase in the size of the nuclei and nucleoli which he believed to be due to a direct stimulating effect of the can moven on these structures. Condr. and Paletta (1941) in a careful study of the pre-cancerous hyperplasia induced in epid rm's by methylcholanthrene observed a progressive increase in nuclear and evtoplasmic volumes of both basal and spinous cells with increased mitosis especially in the basal cells. Increase of nucleolar size took place in the later stages of hyperplasia. Condr. and Piletta felt unable to state whether the increased mitosis in the hyperplastic epidermis was a direct or indirect effect of the caremogen. These workers had found also that intranuclear viscosity measured by the displacement of nuclear contents by centrifu eation was slightly diminished during pre-cancerous hyperplasia and enable diminished in actively carcinomatous cells and that similar changes occurred also in human tissues. They suggested therefor, that changes of extenlasmic and nuclear volumes during careinoeunesis may be related to chances of mineral and water content. Pullinger (1940 and 1941) found that the hyperplasia induced in epidermis by a single application of a careinogenic hydrocarbon appeared to be specific and unlike that following the application of non-carcinogenic substarces. Law (1941) using a race of mice highly sensitive to careinogens applied to the skin obtained multiple pup llomas and carcinomas following single applications of 9 10-directive 1 2 benzanthracen-

Glucksmann (1945) has reviewed previous work on the structural chances in mone skin following applications of cartimogenic hydrocarbons and has carried out further studies on the respons to bearpyren. The primary response comprised increased mito is with increase in both number and size of the cells and delay of differentiation—and these chances affected the whole of the treated are: Papillomas and carteriomas appeared as foculous increased orientation—and lateral expansion of papillomas is a result of increased growth of adjacent hyperplastic reconstanding appeared to be a gradual process since it is impossible to find a clear demarkation line between realternant cells and their non-malicinant reighbours. Even faith small foci are not sharply outlend.

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vascular and other changes in the subepithelial connective tissues. In his experiments invasive carcinoma appeared to develop most usually in relation to areas of damaged elastic tissue and dermal scars.

As to the mode of development of sarcomas following the subcutaneous introduction of carcinogens, Orr (1939) found that, while implanted pellets of paraffin or of paraffin containing non carcinogenic hydrocarbons incited the usual foreign body reaction and were finally encapsulated in fibrous tissue, this was not the case with pellets containing potent carcinogenic substances. The newly developed tissue around such pellets was deficient in quantity and quality and no effective fibrous encapsulation eventurited. The development of sarcoma, which took place in the tissues marginal to and often at some distance from the pellets thus appeared to be related to a deficient or frustrated foreign body response occasioned by the presence of the carcinogen. Other workers also (e.g. Peacock and Beck) have observed that sarcomas may arise from the tissues some distance marginal to the introduced material.

(b) Latent pre cancerous changes

It has been shown repeatedly that, following applications of a carcinogenic hydrocarbon for a limited period, the tissues may then show little or no structural change during a quiescent phase of short or long duration, and yet tumours may subsequently appear. This latent period was subjected to close experimental study by Rous and Kidd and by MacKenzie and Rous (1941) These workers showed that, when tar is applied for a period insufficient to induce tumours in rabbits the epithelium, though thereafter apparently normal and quiescent, has nevertheless received a bias towards future tumour formation is recommenced later for a short period, papillomas may speedily appear Cessation of tarring may now be followed by regression of the papillomas, and a subsequent course of tarring may promptly re evoke them. In this way a particular papilloma may be made to disappear and reappear repeatedly but each time it reappears more promptly and regresses more slowly Finally, no retrogression occurs even when tarring is permanently discontinued, and the papilloma grows progressively and becomes malignant. According to the view of Rous and his colleagues continuous tarring induces a continuous succession of imperceptible stages while intermittent applications induce changes up to a certain point with each applica In the intervening tar free periods, the cells already prepared to become cancerous on slight additional provocation may nevertheless lie quiescent for long periods until the additional provocation of resumed tarring or of some non specific irritant or a trauma, precipitates them into progressive uncoordinated These experimental findings recall and amplify those of Deelman, Pullinger and others already referred to, which show that injury of a carcinogenic ally prepared area may precipitate tumour formation. Lavik and co workers (1942) have confirmed the cumulative effects of successive applications of carci nogens the initial applications produce subcancerogenic changes in the tissues. so that repainting after a long interval may rapidly induce tumours

(c) Co carcinogens and anti carcinogens

The preceding account shows that the application of a carcinogenic hydrocarbon to a susceptible tissue leaves an indebble effect on the tissue such that

subsequent applications of stimuli not in themselves carcinogenic may jet evoke neuplasia. Such stimuli, which may be called co carcinogenic might also operate during the application of the carcinogen itself. Thus, Shear and others have advanced reasons for believing that tars and tar fractions contain substances which reinforce the action of the carcinogenic constituents. and Berenblum (1941) showed that croton oil applied with or after benziptene augmented the potency of this substance. On the other hand carcinogenesis by hydrocarbons is inhibited by mustard gas (Berenblum 1935) and by bromobenzene and certain other halogen compounds (Crabtree 1943).

(d) Effect of carcinogenic hydrocarbons on tissue cultures

No worker has yet proved the induction of neophistic change in tissue cultures treated by carcinogens. The few experiments which have been done were reviewed by Cook and Kenniway (1940) and by Earle and Voeglin (1938) whose own work showed retardation of growth and degenerative changes in cultures of rat and mouse fibroblasts treated with methyletiolanthrene even in low concentrations. Mortion stated that Gey had observed neoplastic change in cultures of rat fibro blasts and that a report was in the press but as far as I know this has not appeared. More experiments in this field are needed. Lewis and Dolynski and Halberstaedter found that pure cultures of a benzpyrene induced rat streom retained their malignant properties in vitro and regularly produced tumours on reinocula tron into rats.

(e) The effect of carcinogenic hydrocarbons on lower animals and plants

This has been the subject of a few scattered observations which briefly summarized by Page by Earle and Vocation and by Cook and Kennaway (1940) have included yeast plant roots hydroids and planarians in all of which some stimula tion of growth has been reported. Of special interest are Mottram's experiments (1941) with paramoecia and other chates treated with earemogenic hydrocarbons and other agents. These protozon showed signs of increased extoplasmic viscosity and various nuclear and mitotic abnormalities and the abnormal organisms transmitted similar abnormalities to their descendants. Mottram looked upon these abnormalities as analogous to the cellular pleomorphism and anapirsia of malignant tumours and suggested that protozoal studies may afford the simplest way of analysing the essential characters of the neoplastic change change may be primarily eytophismic rather than nuclear for the cytophism contains important components such as mitochondna and Golgi apparatus which may be the main points of action of the easeingenic agent. Mottram's views are still in the realm of hypothesis but they justify further research alone the lines he suggested

(f) The chemical changes and fate of carcinogenic indicarbons in the tissues. These were discussed it length in Fieser's paper in 1938. He concluded it seems clear that the hydrocribon suffers rapid alteration in the animal body. Some chemical reaction occurs and this apparenth exhausts most of the carcinogen long before tumors begin to appear. The most obvious hypothesis is that the reaction in which the carcinogen disappears represents the first step in a

time-consuming and complicated chain of events leading eventually to malignant growth Fieser also referred to certain similarities in the chemical properties bile duct cystadenoma, but all combinations of these occurred, and multiple tumours were often seen Miller and Baumann (1945) and Sugiura et al (1945) have shown the carcinogenic activity of several new derivatives of dimethal aminoazobenzene

(3) Henatic tumours produced by other agents

Although the azo compounds are highly active and selective as carcinogens for benatic tissue it is important to recall that they are not the only ones Reference has already been made to tumours produced by locally introduced hydrocarbons and by cutaneous applications of 3 4 5 6 dibenzearbazole Important also is the observation of Edwards (1941) that benign hepatomas can be induced in mice by carbon tetrachloride

An interesting relationship between the carcinogenic substances of the azo class and the polycyclic hydrocarbons is shown by some work of Cook et al They found that 2.2 azonaphthalene could produce liver tumours in mice, and that the allied substance diamino dinaphthyl was still more potent. This substance readily undergoes deamination to 3456 dibenzearbazole, which, as already mentioned when discussing hydrocarbons also produces liver tumours as well as skin tumours and sarcomas at the local sites of application

SECTION III

SUNDRY OTHER CHEMICAL CARCINOGENS

(1) 2-Naphtbylamine and bladder tumours

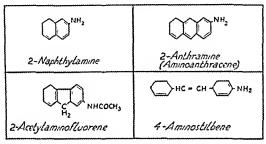
The occupational incidence of papilloma and carcinoma of the bladder in employees in the aniline dye industry was recognized many years before its experimental confirmation by Hueper and co workers in 1938 Many previous workers (cited by Berenblum and Bonser) had attempted, unsuccessfully to produce bladder tumours by means of aniline derivatives and allied substances Hueper and co workers showed that vesical tumours could be induced in dogs by prolonged administration of 2 (Beta) naphthylamine a compound related to aniline and frequently present in aniline products. The specific carcinogenic activity of this substance for the epithelium of the urinary tract was confirmed by Bonser (1943) Hueper's book contains an excellent review of the whole subject of the occupational tumours of aniline workers, and of their experimental counterparts While 2 naphthylamine is the main substance so far incriminated it is very probable that other aromatic amines or their derivatives will also prove to be occupational carcinogens. and it must not be forgotten that, as mentioned above, azo compounds which are unrelated to aniline, can also evoke urinary tract fumours

(2) Other aromatic amines

The discovery of Wilson et al that continued oral administration of 2 acetyl aminofluorene to rats produced epithelial tumours of several different organs, notably the bladder, renal pelvis liver pancreas and lung was confirmed by Bielschowsky (1944) and by Armstrong and Bonser It appears probable however

that different breeds of the same species differ in the localization of the tumours produced. Bielschowsky's Wistar rats showed a high incidence of carcinomis of the liver, breast external auditory meatus and intestines, and also leukacimis while in Armstrong and Bonser's mice carcinomas of the bladder were the most frequent tumours as in Wilson and co-workers rats. Blelschowsky (1945) also obtained adenomas and carcinomas of the thiroid in rats given neetyl minofluorene, and he and Green saw multiple reast carcinomas in a foul.

TABLE III
STRUCTURAL FORMULAE OF CARCINOGENIC ARDINATIC ANINTS



Another aromatic amine recently found to be carcinogenic is 2 anthramine (2 aminoanthracene). By local applications of this substance to rats Bickshowsky (1946) obtained carcinomas, papillom is and spindli-celled tumours of the painted skin, and occasional remote tumours also including carcinomas of the external auditors, meature.

Work in progress by Haddow. Kon and Harris has shown that 4 ammostifbene and several derivatives are categogicus for rats.

(3) A sarcoma producing quinoline-styral compound

While studying the efficies of trypinocidal substances in rice. Browning and co-workers (1933) and 1936 decovered that a complex quinoline stard compound was highly potent in preducing surcomas at the site of the injection.

(4) Adrenal medullars tumours produced by nicotine

In first receiving small dails doses of moutine by subcutaneous injection Similar (1933) observed includar provides of the chromatil a troug of the adrenal plands. I wither work on this interesting result to medial.

(5) Inorganic substances and non-specific irritants

It is probable if it presents to the discrete of the specifically extensions substances, and when the content is an indicate of the specifically extensions which is a simple state of the specifically extensions and the specifically extensions of prophetical transfer of the specifically extensions and when the specifically extensions are substantially extensions.

and metallic salts in an endervour to induce tumours. The occasional positive results reported, as by Narat, are of doubtful significance. Burrows (1936) reported that in none of 362 animals did a tumour grow at the focus of chronic irritation crused by injections of silica, bouillon or starch, but that 53 per cent of these animals which lived 4 months or longer developed tumours at other foci into which dibenzanthracene had been injected.

The recognition of chronic arsenical dermatitis, due to occupational exposure or medicinal administration, as an occasional precursor of carcinoma of the skin led to many attempts to produce arsenical cancers experimentally. The first tumour following the experimental use of arsenic was that of Leitch and Kennaway in 1922, and the most recent that of Hueper in 1942. These occasional positive results, however, are still inconclusive, and further work is needed

The experimental production of teratomas of the testes of roosters by means of intratesticular injections of zine salts, reported by a group of Russian workers, and confirmed by Bagg in America, is of doubtful significance for mammalian pathology. It is discussed in Chapter 61

(6) A review of substances tested for carcinogenic powers

With the constant increase in the number and variety of synthetic organic and other compounds handled and eaten by civilized man, thought must be given to the possible carcinogenic properties of many of these. Already, within the last two decades as we have seen several distinct classes of potent carcinogenic compounds have been identified. It is certain that future research will reveal similar

potency in other classes of compounds as yet not suspected of it

The US National Cancer Institute has recently issued a valuable tabular survey of compounds which have been tested for carcinogenic activity, compiled by J L Hartwell This survey covers 696 substances which have been tested, 169 of which have been carcinogenic. These of course include the carcinogenic hydrocarbons and other compounds described above, many of which were tested in the course of deliberate search for likely carcinogenic agents. The future will witness a great expansion of such biological testing of synthetic substances old and new and of the by products of industrial and technological processes. Hueper's book outlines our knowledge to date and his opening section on the new artificial environment is an arresting reminder of the complexity of the chemical hazards of modern life.

SECTION IV

THE EXPERIMENTAL PRODUCTION OF MAMMARY TUMOURS

(1) Early work on the relationship of ovarian function and mammary tumours

Struck by the fact that tumours of the breast were very common in women and very rare in men and perhaps by the acceleration of growth of mammary cancers during pregnancy and lactation elinicians long ago suspected some relationship between ovarian activity and breast tumours and oophorectomy was advocated and practised as a therapeutic measure in eases of mammary cancer. Experimental researches on spontaneously occurring mammary tumours in animals, and the identification of the ovarian hormones soon led to much more precise knowledge in this field.

Lathrop and Loeb in 1916 found that removal of the ovaries of female mice before the age of six months markedly decreased the subsequent incidence of mammary cancers and that the tumours which did develop in spayed animals appeared at a later age than in normal controls. These effects were not observed in animals spaced at ages exceeding six months. Prevention of breeding also diminished the mammary cancer incidence and increased the age of development of the tumours but less markedly so than spaying Lathrop and Loeb interpreted their results as due to a chemical influence of the corpus luteum on the mamma. an influence which was superimposed on an hereditary factor of tumour suscepti Confirmation of Lathrop and Loeb's experimental results came with the work of Cori (1927), who showed that removal of the ovaries in very young mice of a cancer susceptible strain prevented the subsequent development of breast tumours that castration performed between two and five months of age reduced but did not entirely prevent the development of tumours while castration after six months (i.e. after 30 oestrous cycles) had no effect on the subsequent incidence of tumours

Murray (1928) confirmed the diminution of the incidence of breast cancer in mice following early gonadectomy or by enforced virginity—and also showed that while intact or castrated males never developed breast tumours castrated males into whom ovaries had been grafted developed tumours in 7 per cent of cases

(2) The experimental production of mammary carcinoma by oestrin

The discovery in 1929 of methods of preparing ovarian oestrogenic hormones in a pure form opened the way to more exact study of the problem of the association between ovarian activity and the genesis of cancer of the breast

In 1932 and 1933 Lacassagne obtained mammary carcinomas in male and female mice by giving large weekly subcutaneous injections of oestrone benzoate This result which was soon confirmed by Burrows (1935) and others (summarized by Cook et al. 1936 and by Cramer. 1940) constitutes a major landmark in the history of cancer research. For it affords the first discovered instance of a carcino gen of endogenous nature. In male mice treated with ostrin prior to the development of neoplasms the breasts show varying degrees of hyperplasia and cystic change, closely resembling those of so-called chronic cystic mastitis in the human breast (Burrows Bonser).

That the intrinsic susceptibility of mammary epithelium to neoplasia influences the production of tumours by oestrin was shown by the results of Lacassagne Bonser and others. Thus, applying large doses of oestrone to male mice of cancer susceptible and cancer resistant strains. Bonser observed carcinomas supervening on hyperplasia of ducts and acini in the former but only hyperplasia without carcinomas in the latter. On the other hand, the same worker in later experiments (1937) succeeded in inducing mammary cancers in female mice of a strain not subject to the development of mammary tumours.

In an outline of the hormonal actuology of breast cancer. Cramer summarized experimental evidence which showed that the carcinogenic power of oestrin for manmary tissue was augmented by the adreno-cortical hormone and antago nized by the anterior pituitary thyrotropic hormone by an adranal medullary hormone and by the male sey hormone, testosterone.

Observations of the pathological effects of oestrin overdosage on the mammary tissue of animals other than mice are so far few Heiman (1937) after giving in account of a spontaneous mammary careimoma in a rabbit, a species which rarely develops such timours, described the production of hyperplastic cystic and papillomatous changes in the breasts of old female rabbits by subcutaneous injections of antuitin S and oestrin, but without careimomatous changes even after prolonged treatment

(3) The destrous cycle in relation to the incidence of mammary caremoma

Since the incidence of spontaneous mammary careinoma varies greatly in different strains of mice and since different strains also show marked variations in the oestrous cycle the possibility of there existing a relationship between these two called for investigation. The work of Bonser (1935) and of Burns et al. (1936) however has shown that there is no parallelism between any of the features of the oestrous cycle and the incidence of mammary tumours. The high incidence of mammary cancer in certain inbred strains of mice is not accompanied by any noteworthy peculiarities of the sexual cycle, the infrequency of tumours in other strains obtains in spite of the stimulation of oestrin with each oestrous cycle during reproductive life. As the experimental production of mammary carcinoma by Lacassagne and others has shown however, oestrin overdosage may cause tumours in even cancer resistant strains.

(4) Reproductive overactivity, duct stasis and mammary cancer

That purely local as well as hormonal factors also operate in the causation of mammary tumours was shown by Bagg (1925 and 1936). In a strum of mee of low tumour medence he obtained many tumours by rapid breeding accompamed by milk stasis achieved by either non suckling or by ligation of ducts Later (1939). Bagg working with Hagopian confirmed and extended his original results using rats. In these animals also rapid breeding and the prevention of suckling markedly increased the incidence of mammary carenoma fibro adenoma and adenoma and in some of the rats with mammary tumours pituitary adenoma, hyperplastic adrenal glands or uterine lecomyomas were also present. In some of the animals several different kinds of mammary tumours coexisted. Duct stasis was a prominent feature in these experiments as in Bagg s earlier ones, and the authors suggested that chemical irritation from retuined secretions may have been the immediate cause of the timours.

Confirmatory of the influence of local mjury to the mammary ducts in the causation of mammary cancer were the experiments of Fekete and Green (1936) Using a strain of mice in which 80 per cent of parous females developed minimary cancer equally upon the two sides these workers found that if the right sided nipples were touched with a hot wire, and the mice then allowed to breed 70 per cent of the tumours which later developed in the breasts were in the injured right sided organs.

(5) The possible mechanism of production of experimental mammary tumours

It is possible that the production of mammary tumours by oestrin overdosage is brought about partly by local factors similar to those responsible for Bagg s

results Oestrin overdosage first produces hyperplastic and cystic changes resembling those of so called 'chronic mastitis in the human subject and in the experimentally produced lesion as in the spontaneously occurring human one duct obstruction and retention of secretions are often prominent features. Perhaps then the mammary hyperplasia induced by oestrin is finally provoked to neoplasia by a chemical stimulus from these retained secretions as suggested by Bagg. Further, it is not impossible or even unlikely that this stimulus may be due to specific carcinogenic substances generated in the stagnant duct contents. The abundant creamy or pultaceous material often seen in dilated ducts in the human breast is rich in faitly and hypodal substances and the slow degradation of these under suitable conditions might involve the formation of circinogenic compounds related to those discussed in Section I of this chapter. A search for such substances in retained mammary secretions is needed.

(6) Heredity and nursing factors in mammary cancer

More than once we have already referred to the fact that different stocks of mice differ in the incidence of spontaneously occurring minimary carcinomas. By close inbreeding from mice of high enneer incestry it was found possible to obtain strains with an extremely high incidence of breast tumours. In some strains 80 per cent or more of parous females developed tumours. On the other hand by close inbreeding from mice of cancer free ancestry a race of animals which rarely or never showed spontaneous breast tumours could be developed Differences in the incidence of spontaneous mammary cancers in different inbred strains of animals were therefore interpreted as dependent on hereditry factors which it was assumed determined differences in the susceptibility of the mammary epithelium to cancer evoking stimuli. A surprising fact which was soon apparent however was that maternal influences were more important than paternal in the transmission of this susceptibility.

That the different susceptibilities or insusceptibilities of inbred mice to the development of mammary neoplasms do not reflect purely genetic differences was shown by the work of Bittner summarized by him in 1940 1942 and 1944 This worker found that the incidence of breast cancer in mice was markedly influenced by the source of the milk on which they had been fed. Mice which had been suckled by females of a stock with a low incidence of breast cancer also showed a low incidence and vice versa. Thus in one experiment, while a control group of non fostered female mice of a high-cancer stock eventually developed breast cancer in 84 per cent of cases female mice of the same stock. but suckled by foster mothers of low-cancer stock, later developed tumours in only 7 per cent. Nursing had no such influence on the subsequent incidence of lung tumours Bitiner concluded that the development of breast cancer in high cancer strains of mice is probably due to a combination of three factors (a) breast-cancer producing influence transmitted through the milk of mothers of cancerous stock (b) an inherited genetic susceptibility to breast cancer and (c) a hormonal factor affecting the breast. He also believed the milk factor to be fully as important as the genetic factor in the equisation of breast cancer. The nature of the milk transmitted influence whether an enzyme or a chemical agent or a virus, remains undetermined, but it is known to be present, not only in the milk, but in tumour tissue and other tissues of high cancer mice, and to retain its potency in filtrates and in desiccated or glycerinated tissue. (For further details regarding the mammary tumours of mice and their experimental study, see the Symposium by the Staff of the National Cancer Institute, Washington, 1945.)

SECTION V

THE HORMONAL PRODUCTION OF TUMOURS OTHER THAN MAMMARY

The experimental production of mammary tumours by oestrin was followed by reports of the production of tumours of other endocrine or endocrine controlled tissues by similar means. Although the experiments are so far few, the results are of great interest and show that an important new field of research has been opened up. Following oestrin overdosage, true tumours or tumour like proliferations have been observed in many organs, notably the testis, uterus, pituitary gland, prostate and thymus. (For additional details, consult Burrows s book on sex hormones, 1945.)

(a) The testis

Following the observation of Burrows (1935) that hyperplasia of the interstitial cells of the mouse s testis resulted from the administration of oestrogens, Bonser and Robson (1940). Bonser (1942 and 1944) and Hooker and Pfeiffer (1942) obtained true interstitial cell tumours in mice by this means. Although initially innocent and closely resembling spontaneously occurring interstitial cell tumours in animals and man, some of these growths eventually displayed malignant characters and produced metastases. The incidence of testicular tumours resulting from oestrinization varies with the strain of mice used, it is not affected by foster nursing and there is no p trallelism between the number of testicular and mammary tumours produced (Bonser, 1944)

(b) The uterus

Of the many reports of cancerous or pre cancerous changes in the uterus following prolonged over-oestrinization the most notable are those of Gardner et al (1938), Suntzeff et al (1938) Pierson (1938) and Allen and Girdner (1941). The principal changes reported have been proliferation and squimous metaplisate of the uterine glands and their deep penetration into the muscle mainly in the cervical region. In some instances these changes may not have been neoplistic but rather extravagant hyperplasias of the nature of endometriosis but in other cases e.g. those of Allen and Gardner, there is little doubt that they were true tumours. Much more work is needed to elucidate the part played by hormones in the genesis of uterine carcinomas and the factors determining the transition from hyperplasia to neoplasia.

Lipschutz and co workers have published many papers on the production of multiple "fibroids' of the uterus and of the extra gential peritoneal tissues in guinea pigs following prolonged administration of oestrogens. Although large growths were obtained their neoplastic characters are open to doubt since they retrogressed on cessation of treatment. Nelson also observed fibromyomas of the uterus in oestrinized guinea pigs.

(c) The pituitary

Cramer and Horning (1936), Burrows (1936), Zondek (1938) and others have observed large tumour-like overgrowths of the anterior pituitary in mice of rats following prolonged administration of oestrogens. Proof of the truly neophystic character of these will depend on showing that they continue to grow progressively after cessation of treatment.

(d) Other tissues

Cramer (1940) mentioned examples of careinoma of the prostate and tumours of the thymus seen in oestimized animals. Burrows a studies of the hyperphisia and metaplasia induced in the prostate by oestim should be recalled. It remains for future research to ascertain if, and under what conditions, hormonal disturbiances may be provocative of true tumours in tissus which like the prostite, are under hormonal influences or in the various endocrine tissues themselves. An important warning regarding the experimental hormonal production of tumours must be added here. In many of the experiments cited above the hormone dosagus were refutively enormous, so that applicability of the results in human pathology must be assessed with due caution. However, that the results are of significance especially as pointers to lines of future experimental and endocrinological ruserich cannot be doubted.

SECTION VI

THE EXPERIMENTAL PRODUCTION OF TUMOURS OF THE LUNGS

In Section I we have already described the increased incidence of tumours of the lungs in mice after the administration of carcinogens by various routes. This is attributed to absorption into the circulation and carriage of these substances to the lungs by that route. While we must not overlook the possibility of such remote action in the causation of lung cancer it is clearly important to ascertain whether lung tumours can be produced by the direct inhalation of carcinogenie substances in the form of dusts smokes or gases. Many experiments of this kind have been performed using soots bituminous smokes tobacco smoke chaust gases from internal combustion engines powdered pitch dusts from tirred roads, silicious and metallic dusts radio active dusts, and pure circinogenic hydrocarbons in powdered form.

(I) Experiment with soots, smokes or exhaust gases

These experiments, typical of which have been those of Schmidtmann (1930) studies and Haythorn (1937) and Sedig and Benigaus (1936 and 1938), have given negative or equivocal results. Thus Sedig and Benigaus in a first experiment appeared to obtain a significant increase of lung tumours in mice inhalmg bituminous soot, but were unable to confirm this result using a dust composed of lamp black mixed with crutinogene tar. Schauter and Haythorn obtained no lung tumours following exposure of animals to coal smoke, and Schmidtmann land a similar negative result with the word from a Diesel engine. The results with tobacco smoke also have been moonulative, although tobacco tar has been

shown to be carcinogenic when applied to the skin (Flory, Rosso). Experimental work, then has so far failed to prove that soot and organic smokes play a part in the genesis of lung tumours. It is of course possible that further experiments, using more suitable smokes and longer times of exposure, may still yield significant results.

(2) Experiments with dusts from tarred roads

Of particular interest are the researches of Campbell (1934, 1937, 1939 and 1942) on the carcinogenic effect of inhaled dust from tarred roads This worker found that prolonged exposure of mice to such dust greatly increased the incidence of lung tumours—in one of his experiments nearly tenfold. At the same time most of the dusted mice developed cancers of the skin, evidently due to the tar present in the dust, since tar extracted from the dust with benzene was carcinogenic The tar was not the only component of the dust responsible for the production of lung tumours, however, since mice exposed to the tar free residual dust after benzenc extraction still showed an increased incidence of lung tumours, though to not so great an extent as when the tar also was present. In subsequent experi ments (1942) Campbell used dust obtained from the same road surface five years after it had been tarred. This dust was much less active than the cartier sample as regards the production of skin tumours, but it still caused a pinefold increase in tumours of the lungs. The deduction to be drawn from Campbell's results is that, while the tar component of road dust is one fretor in increasing the incidence of lung tumours in dusted animals it is not the only, nor necessarily the most important, component attention must be given also to the inorganic constituents of the dust, which include silies, oxide of iron and aluminium oxide

(3) Experiments with inorganic dusts

In his 1940 experiments, Campbell found that dusting with precipitated silica or with iron oxide trebled the incidence of lung tumours in mice living ten months or longer. Subsequent experiments (1942) confirmed the careinogenic effect of dusts containing silica and oxide of iron, and also demonstrated that steel grindings had some potency. Experiments carried out with radio active urrinium-rich dust from the Joachimsthal mine gave a decided increase in lung tumours, though not strikingly greater than with some of the other dusts tested. Campbell pointed out that the prevalent view that lung cancer in the Schneeberg and Joachimsthal miners is due to radio active substances is still unconfirmed experimentally, other factors may be involved as well.

(4) Conclusion

Campbell's researches point clearly to the importance of inhaled substances in the genesis of lung tumours. It is for future experimental research to make more precise our knowledge of the carcinogenic activity of various occupational and other dusts inhaled by human beings, and to determine the particular ingredients of these which are mainly responsible. Enough has already been done to show that both organic and inorganic substances will be incriminated, and to indicate the methods to be pursued in research in this field. In addition, the

that such a substance is formed from the cholesterol in irradiated skin. However there is no conclusive evidence of this, Bergman et al found no carcinogenic activity in irradiated cholesterol applied to the skin of mice

Hueper drew attention to the great variety of structure displayed by actinic

carcinomas of the skin of rats

(2) The experimental production of tumours by X-rays

Rontgen's discovery in 1895 was soon followed by the appearance of cases of chronic X ray dermatitis in exposed persons, and examples of supervening carcinoma of the skin begin to be reported from 1902 onwards (references by Hueper) Experimental confirmation of the carcinogenic effects of X ray irradiation has been made by several workers notably Schurch (1930) who carried out it detailed histological study of all stages of the development of carcinomas of the ears of rabbits exposed for long periods to X rays. In these experiments, is in their human counterparts tumours have usually appeared only after relatively long periods of exposure, for example, in Schurch's rabbits two years or longer

The occasional development of sarcomas in persons over exposed to X rays, usually following Rontgen treatment of tuberculous lesions (Hueper, 1942) has also been parallelled experimentally. As long ago as 1909, Marie and coworkers obtained a spindle celled sarcoma in the rat s cutis after prolonged irradiation, a result repeated by Bauer in 1937. Licassagne and Vinzent (1928) and 1929. Burrows and coworkers (1937) and Burrows and Clirkson (1943) obtained sarcomas of tissues which had been made the site of chronic inflammation artificially. The English workers produced subcultaneous spindle celled growths by irradiating the site of injections of silica and kaolin. Chronic inflammatory tissue is thus more susceptible than normal connective tissue to the development of sarcomas following exposure to X rays.

(3) The experimental production of tumours by radio active substances

Most of the tumours produced by radio active substances, either in man or experimental animals have been sarcomas, but a few carcinomas of the skin undoubtedly due to radium have been reported

The first recognized instances of human sateomas due to radio active materials were the occupational sarcomas of bone due to radium and mesothorium ibsorbed by workers using luminous paints. The remarkable story of this occupational tumour reported first by Martland and Humphres in 1929 and later by Martland, will be fully described in Chapter 43. No occupational sarcomas in soft tissues due to radio active substances have so far been reported, but Norgaard described an instance of fibrosarcoma of the tibia due to intra articular injections of radium chloride for therapeutic purposes.

Experimental sarcomas of soft tissues and of bones have been produced by many workers by means of radio active substances Daels (1926) and Daels and Biltris (1931) obtained subcutaneous sarcomas in rats and mice following the intro duction of small amounts of radium salts in glass tubes. Ross confirmed this, using radium adequately screened in platinum, thus proving the sarcoma evoking power of pure gamma rays. Sabin and co workers obtained osteogenic sarcomas in 2 of 7 surviving rabbits following repeated intravenous injections of radium and mesothorium thus establishing the experimental counterpart of the occupational

sarcomas of workers with radio active paints. Schurch and Uehlinger reported the frequent development of sarcomas following the direct introduction of radium and mesothorium into the femurs of rabbits. Dunlap et al. (1944) obtained transplantable osteogenic sarcomas by feeding rats with radium.

In view of the use of Thorotrast (colloidal thorium dioxide) in radiodiagnosis the ready experimental production of sarcomas by subcutaneous or intraperitoneal injections of this substance is of special interest (Roussy et al. Selbie, and Foulds) While no tumours following the use of Thorotrast in man have yet been recorded the risk that such may appear during the next decade or more when due time has elapsed following the use of this relatively recent method of diagnosis, must be recognized. It is noteworthy that not only sarcoma, but also carcinoma, may be caused by this substance, in one of Foulds's guinea pigs, which received injections into the base of the nipple, a transplantable marinmary carcinoma with metastases developed.

SECTION VIII

PARASITES AS CARCINOGENIC AGENTS

The student approaching the subject of tumour causation is perplexed by the diversity of opinions regarding the causative role of various parasites. The views, once widely held that tumours were caused by specific protozoa or fungi, have long since been discarded, and although syphilitie glossitis clearly predis poses to carenoma of the human tongue, and although tumours do sometimes supervene on various other chronic inflammatory lesions none of the ordinary pathogenic bacteria have been incriminated as carcinogenic. As regards metazoal parasites doubt has been cast on the once widely accepted carcinogenic properties of the nematode called by Fibiger Spiroptera neoplastica—but there is no doubt that some other parasites notably cysticercus in rats—can induce true tumours. Modern research has disclosed more clusive parasites filterable viruses which are responsible for certain special classes of tumours and the volume of published work in this still unsettled field has become disconcertinely great.

(1) Fibiger's 'Spiroptera neoplastica

In 1913 Fibiger described what he believed to be earcinomatous growths in the forestomach of rats infested with a small inematode, which was accordingly called Spiroptera neoplasticar or Gonghomena neoplasticum. The adult parasites reside in the stratified epithelial mucosa of the tongue oesophagus and fore stomach. Ova discharged in the facees and eaten by a certain species of cockroach reach and become encysted in the strated muscles of this intermediate host. The cycle of development of the parasite is completed when rats eat infected cockroaches. Heavy infestation of the rat's forestomach produces luige multiple appillary epithelial overgrowths. According to Fibiger these growths in his experiments eventually became mahgnant infiltrating the wall of the stomach and producing metastases in lymph glands and lungs. Fibiger also reported cancers of tongues infested by the parasite.

Although Fibiger's results were widely accepted as the first experimental

production of malignant tumours, his interpretation is open to doubt. As long ago as 1918, Bullock and Rohdenburg showed that carcinoma like papillary overgrowth of the rat's stomach could be easily induced by simple mechanical injury and that squamous metaplasia in bronchial epithelium in the very frequent chronic broncho pneumonia affecting rats may produce pictures similar to those of the suspected pulmonary metastases in Fibiger's rats. They therefore questioned Fibiger's claim to have produced true tumours. Subsequent workers also have failed to obtain genuine tumours by means of the parasite, and Passey et al advanced evidence that the epithelial overgrowth in Fibiger's rats was partly the result of vitamin deficiency, and that, as Bullock and Rohdenburg had suggested, the lung lesions thought by Fibiger to be metastatic growths may well have resulted from bronchiectasis and metaplasia

(2) Cysticercus sarcoma of the rat's liver

Following the papers of Bullock and Rohdenburg (1916 and 1917) on the association of parasitic cysts with sarcomas of the rat s liver, Bullock and Curtis (1925) used the parasite for producing these tumours experimentally. The parasite C₃ sticercus fascolaris, is the cystic form of the cat tapeworm, Taenia crassicollis, and by feeding rats with the eggs of this worm, Bullock and Curtis obtained single or multiple tumours of the livers of 1400 rats. The sarcomas developed from the connective tissue walls around the cysts, the main types were spindle celled or polymorphous celled, but there were some fibrosarcomas one lipo sarcoma, and cartilaginous tissue was present in several tumours one of which showed cartilage also in its peritoneal metastases

(3) The Rous sarcoma and other filterable tumours of birds

Since their first discovery in 1910, these peculiar tumours have been the subject of intensive research producing an enormous volume of papers. Only the barest outline can be attempted here, for further details the reader should consult the excellent review by Foulds (1934) and the papers of Rous and co workers (references by Rous 1935)

In 1910 Rous found that a transplantable sarcoma of the domestic fowl, now known as Rous sarcoma I', could be transmitted by cell free filtrates Other distinct fowl sarcomas similarly transmissible were soon discovered. These differ decidedly from one another in both histological structure and behaviour, and there is general agreement that the filterable agents responsible for them are distinct and will evoke only growths of the same kind as those from which they are derived. It is therefore improper to speak of all filterable tumours as "Rous sarcomas", this obscures the differences between the several tumours

In transmission by grafts the resulting tumours appear clearly to be derived wholly or predominantly from the implanted cells, but in cell free transmission the tumours arise of course from the cells of the new host. The precise histo genesis of the filterable tumours whether they arise mainly from fibroblasts, monocytes or fixed endothelial cells, is controversial and is perhaps not material in view of the probable intermutability of these allied mesenchymal cells. Certain it is that all of the tumours are sarcomatous of birds has proved to be filterable.

Filtrates differ greatly, and often unaccountably in potency. The more malignant growths, such as Rous sarcoma I, usually yield active filtrates but filtrates of the less malignant tumours are often innetive. Even sarcoma I filtrates may be obstinately inactive for a period, and then filterability may spontaneously return. The susceptibilities of the agents to antiseptics and heat resemble those of living agents but they appear to have 1 high resistance to ultra violet rays, X rays and radio active substances. Ultrafiltration centrifugation and electron microscopy show that the agents are particulate, and that the mean size of Rous sarcoma I particles is about $50\mu\mu$. During the growth of a tumour there is a concomitant increase in quantity of the agent.

Much interesting work has been done on the antigenic properties of the filterable agents, but interpretation of the results is still debatable on many points. One remarkable observation, recorded by Ames and co workers (1940), must be mentioned. Rous agent is neutralized not only by the serum of rabbits treated with the agent itself as antigen, but also by the serum of rabbits treated with normal fowl serum or tissues as antigen and, both anti agent and antifoxl seria are deprived of their neutralizing properties by contact with normal chicken embryo. Hence the agent of Rous sarcoma I appears to contain in addition to a specific antigen a second antigen also present in fowl tissue, a relationship quite peculiar in virus serology.

Tumour producing activity has often been demonstrated in the blood or other body fluids of tumour bearing birds and it has been found that the agent may be localized from the blood stream and may produce secondary tumours in injured or inflamed tissues. Yet it is certain that spontaneous meristases usually do not arise in this way, but result from embolic dissemination of tumour cells as with mammalian tumours. There is no evidence that the tumours are infectious normal fowls do not develop tumours when kept with tumour bearing birds or when fed with tumour tissue.

The transmissible leucoses of fowls are clearly closely related to the filterable tumours they can be transmitted by cell free material and they may occur in association with surcomatous tumours

With rare exceptions sarcomas induced in fowls by chemical carcinogens have proved to be non filterable. The few instances in which filterable tumours have occurred are of uncertain explanation—accidental contamination of the injected carcinogen by agent may have been responsible. Further work is needed in this field.

Have the filterable tumours of birds any bearing on the causation of mammalian tumours? In spite of much debate this question is still unanswered. To those who incline to the virus hypothesis of tumour causation in general the filterable tumours appear as a prototype and as the most favourable material for elucidation of the problems of causation—and they explain the failure to demonstrate filter ability in mammalian tumours as due to permanent inactivation or masking of the responsible agents in filtrates just as Rous sarcoma filtrates may show unaccountable phases of inactivity. Those however who see much of occupational cancer in man or of experimental chemical careinogens are more likely to regard the filterable tumours as probably constituting a quite special class of diseases peculiar to birds. Certain it is (a) that the filterable aruan agents differ from all

other carcinogenic agents in that they can induce only the precise kinds of tumours as those from which they came, and that they multiply in the tumours which they originate, and (b) that these agents are demonstrable only in certain tumours of mesenchymal tissues and never in epithelial tumours in birds

(4) The Shope tumour of rabbits

In 1933 Shope and Hurst found that papillomas of the skin of the cotton tail rabbit were transmissible by cell free filtrates or by glycerinated tissue to both cotton tail and domestic rabbits. The papillomas so produced grew to large cauliflower like masses. The tumours could be passaged repeatedly in cotton tails but only one or two passages could be made in ordinary rabbits. In the cotton tail the papillomas rarely become malignant, but in the domestic rabbit they frequently become carcinomatous within two years (Gya. 1938) Of great interest is the fact that filtrates of the carcinomatous tissue are inactive. Rous found, however, that successful transplantation of carcinomatous tissue, apparently devoid of virus, to fresh host rabbits was followed by the appearance in their sera of an immune body which neutralized papilloma virus. This result suggested that the carcinomatous tissue, though incapable of yielding active filtrates, never theless contained the virus in a masked or inactive form. Further elucidation of this problem is needed. A valuable account of the Shope tumour was given by Rous in his Harvey lecture in 1935

Experiments by Rous on the combined effect of Shope virus and a chemical carcinogen are of interest. It was found that if rabbits were painted with tar until papillomas began to appear, and were then given intravenous injections of Shope virus active papillomas or carcinomas developed in the tarred areas much more quickly than in control tarred animals which had received no virus. This result suggested that the chemical carcinogen had conditioned the tissue for reception of the virus which then precipitated the neoplastic change. Rous and Friedwald found that chemical carcinogens caused rapid cancerous change in

Shope papillomas

Whether deductions drawn from the behaviour of the Shope tumour and its virus are applicable to mammalian tumours generally, only future research can decide So far, the evidence would suggest that this tumour is a peculiar one, and that no hasty conclusions regarding tumour causation in general should be drawn from it

Stanley has found that the Shope virus is a macromolecul ir protein which can be isolated in a crystalline form and he regards it as a pathological protein formed autocartifyically within the cells

(5) Lucke s adenocarcinoma of the frog's kidney

| In his interesting studies of renal observed acidophil intra nuclear inclus | | frogs, Lucke |
|---|-----------------|--------------|
| of a virus Experiments showed that | | |
| | | with liv |
| tumour tissue or with desiccated or | | d by |
| development of characteristic renal tu | mours in 20 per | an 👊 |
| a percentage much higher than in c | No tumo | the ! |
| of inoculation and no tumours | i in alien | 7 ' |
| | | |

concluded that his tumour is probably due to "an inclusion forming, organspecific virus

SECTION JX

ENDOGENOUS CHEMICAL CARCINOGENS

The close chemical relationship between the carcinogenic hydrocurbons of the benzanthracene group and some naturally occurring biological substances such as the bile needs and the sterols has naturally led to speculation as to the possible formation of carcinogens in the tissues themselves. It is quite feasible that in suitable pathological conditions, abnormal metabolic or degenerative products may include carcinogenic substances. I have already mentioned the possibility that this may occur in the contents of obstructed breast ducts and it is not difficult to think of other possible instances. Perhaps in the fall stones which are usually present in the cancerous gall bladder a caremogenic substance has been slowly generated perhaps this has happened also in the smegma retained under the prepuce of the cancerous penis, perhaps the sebaceous contents of a cystic teratoma of the ovary in which careinoma has supervened has developed exercino genic properties perhaps the proneness to malignant change following syphilis of the tongue or eysticerous infection of the liver is due to carcinogenic metabolic products neculiar to those inflammations

The research of the future will certainly include attempts to isolate pure carcinogenic substances from these and other conditions. While no such endo genous carcinogens have so far been identified, there is already substantial experimental evidence of their existence. For example, it has been found that suitable extracts of normal or of diseased incrs are feebly careinogenic (see Kleinenberg et al., 1940 and 1941) and that this property is more pronounced in extracts of livers of cancerous patients and in extracts of livers of races unusually hable to hepatic cancer-for example the African Bantus (des Ligneris, 1940 Hieger 1940 Steiner 1942) Recall here also the discovery of Kennaway and co workers that under certain conditions desoxycholic acid may be encinogenie

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CHAPTER 5

THE STATISTICAL STUDY OF THMOURS

The most voluminous, and in general least reliable, of the main sections of the literature on neoplasms is the statistical. A spate of papers flows unceasingly into a hundred journals and its very bulk prohibits its piecemeal assimilation. Fortunately, however, by the application of certain simple tests of reliability, much of it can be dismissed at a glance. This chapter is concerned, therefore, not with a minute critical analysis of many published papers, but with the formula tion of some general rules regarding the degree of reliability of cancer statistics of various kinds.

I advise the reader to whom the subject is not familiar to read Bashford's and Murray's classical critique (1905), and to study the excellent papers of Wells (1927 and 1931) and Cramer (1937), the one stressing the many sources of error in cancer statistics, the other indicating the ways in which statistical research rightly prosecuted, has been and might be of value Hill's valuable book (1939) on medical statistics especially Chapters 14 16 on common fallacies, should also be read

' CANCER" AN ILL DEFINED HETEROGENEOUS GROUP OF DISEASES

Many statistical writers discuss "cancer" as a whole, tacitly ignoring the vague meaning of this word and the great variety of diseases it embraces. Most of such writers clearly use cancer as synonymous for all kinds of malignant tumours. But as shown in Chapter 3, the distinction between 'innocence" and 'malignant maney" is an indefinite and arbitrary one, almost every histogenetic group of neoplasms displaying a range of behaviour from "benign" to "malignant' Gliomas, basal cell epitheliomas of the skin the so called 'mixed' salivary tumours, many of the papillary growths of the bladder, ganglioneuromas, are examples of neoplasms which might be, and indeed have been, included under the term "cancer" by some writers and excluded by others. To have biological validity, statistical studies purporting to embrace 'cancer" as a whole should include all tumours. To restrict such studies to those tumours only which have been labelled malignant" in clinical records or on death certificates is to commit the statistical crime of making an arbitrary selection of part only of the relevant material

But further, to discuss cancer definable, would have little value diverse entities as inflammation? "Cancer" embraces fully as many and as and statisticians have, rightly, not deemed it useful to make analyses of inflammatory diseases as a whole. To lump together for statisticial study a heterogeneous collection of tumours containing such different diseases as gloomas of the brain, carcinomas of the stomach and teratomas of the testis is no more sensible than it would be to lump together a heterogeneous collection of bacterial inflammations containing such diverse diseases as erysipelas, typhoid fever and tuberculosis

Clearly statistical analysis can be applied usefully only to well defined homogenous groups or species of tumours. If rehable figures can be established for these, then any appropriate summations of these figures which may be deemed

useful can be made. Cramer emphasizes the necessity of recording the data for the medence of cancer in man separately for each tissue or organ. Sweeping statements about cancer in general, without clear specification of the constituents included and evidence of the degree of reliability of the figures for each constituent, are valueless. At the present time, we cannot have reliable figures of the frequency and trend of cancer as a whole because, as will be shown below, available, estimates regarding many of the major constituent groups of tumours are widely maccurate.

DEGREE OF ACCURACY OF DIAGNOSIS

It is an axiom that the prerequisite of any statistical investigation is accuracy of the primary data. Principal of the primary data in tumour statistics are the pathological diagnoses of the cases studied if any considerable proportion of these are erroneous or uncertain then the entire research is vitiated at its outset Application of this basic principle will result in prompt rejection of many published statistical studies. When a writer fails to specify clearly the nature of his material, the bases of the diagnoses made, and the degree of diagnostic accuracy attained, it is a waste of time to study his analyses further.

The fundamental data of statistical cancer research—the diagnoses made by clinicians and pathologists—have very diverse degrees of accuracy. There are

four ascending grades of diagnostic precision

Grade 1 Diagnosis by simple physical examination only

Grade 2 Diagnosis by physical examination supplemented by special methods

Grade 3 Diagnosis by histological examination of surgiculty removed tissues

Grade 4 Diagnosis by necropsy, (a) without histological confirmation
(b) with histological confirmation

These grades of accuracy are of the first importance in assessing the reliability of any series of cases examined statistically—and their meaning and importance must be made elear—

Grade 1

Grade 1 comprises diagnoses made by practitioners from simple physical examination of the pritients, without resort to special diagnostic methods—pathological, radiological endoscopie or operative. Minju diagnoses made by general practitioners, and appearing on death certificates fall into this class. Their degree of reliability is very variable often low and in any case incapable of assessment, varying with the oblity and experience of the practitioner the nature of the disease and the nature of the community. The purely clinical diagnosis of external cancers e.g. carenoma of the breast or of the lip is much more reliable than that of internal cancers e.g. carenoma of the stomach or of the lung. Some quite common internal tumours are so difficult to diagnose hy simple physical examination that many general practitioners think of them erroneously as rainties e.g. carenoma of the lung cerebral glooma. Except when they are more fully investigated by specialists very few of these tumours are diagnosed correctly and the supposedly increased frequency of such tumours during recent vears is undoubtedly due largely to increase recognition hy

practitioners of the need for enlisting the aid of special methods of investigation in suspect cases. The nature of the community greatly affects the accuracy of diagnosis, this is highest in urban communities with experienced specialists and ready means of transport, lowest in remote rural areas with few and scattered practitioners and poor transport facilities. "The motor car, by shortening the distances between patient and physician, unquestionably increases greatly the number of recognized cases of cancer" (Wells)

Grade 2

Grade 2 comprises clinical diagnoses made after supplementing simple physical examination by special physical or chemical methods of investigation—patho logical radiological, endoscopic or operative, but without pathological study of excised tissues. In the hands of experienced specialists, these methods greatly enhance the accuracy of diagnosis of many internal tumours, especially those of the alimentary canal, urinary tract, lung and central nervous system. However, in the absence of pathological examination of excised tumours or of biopsy fragments, an important degree of diagnostic error still obtains with some of these classes of tumours. Many hospital cases fall into this grade of diagnostic accuracy.

Grade 3

Grade 3 comprises diagnoses made after histological examination of excised tumours or pieces of tumours. Histopathological diagnosis of surgical material is sometimes final and complete as for example from examination of an excised cancerous breast or stomach or kidney, or even of small biopsy fragments of such tumours or it may still be incomplete, as when examination of an enlarged lymph gland or of pieces of issue from a tumour in the brain or in a bone or in the peritoneal cavity proves the presence of metastatic carcinoma or of some other neoplasm but still leaves its primary origin undetermined. Further not all histopathologists are of equal ability and experience, questionable diagnoses and archaic terminology are far from rare

Grade 4

Grade 4 comprises necropsy diagnoses Here also, the reliability of such diagnoses depends on the competence and experience of the investigator. Unreliable post mortem work is all too common and incomplete necropsies can, and frequently do, lead to erroneous diagnoses. Even competent pathologists can make occasional mistakes in diagnosis through incomplete examinations especially failure to preserve sufficient or appropriate material for subsequent histological study. I strongly maintain that any post mortem examination, unconfirmed histologically, is incomplete, not infrequently, microscopic examination surprises the clinician and pathologist by showing the faisity of the initial post mortem diagnosis even in cases where this appeared certain. Admittedly, diagnostic errors of this kind are not frequent with such familiar turrours as carcinomas of the breast, of the stomach of the mitestines or of the uterus. Yet, even with these, errors do occur. e.g. my own necropsy records contain instances of the following corrections of post mortem diagnosis necessitated by microscopic

examination— gastric carcinoma to "chronic ulcer", and nee versa, "carcinoma of the colon" to diverticultus, and nee versa actionoma. Vi sarcoma of the stomach intestine breast and uterus. For many venrs, I have made it my practice to confirm microscopically all tumour diagnoses made post mortem. Clearly, for correct identification of tumours of the less frequent and familiar kinds competent microscop estudy is essential. Experienced pathologists are, of course aware of all of the foregoing considerations, and the number of mistaken post mortem diagnoses which they will make should be statistically negligible.

Many large collections of tumour cases dealt with statistically most notably the registered deaths from cancer, are mixtures of all four grades of diagnostic precision, with the lower grades. I and 2 predominating. How much reliance can be placed on such mortality figures? Several writers conveniently summarized by Wells, have attempted to assess the degree of error in clinical cancer diagnosis as disclosed by necropsies in large series of hospital cases. These revealed diagnostic errors in from 27 to 43 per cent of cases—errors not merely of detail but concerning the presence or absence of malignant disease or its nature and primary site. Cleland's necropsy work (1942) disclosed—cancer correctly diagnosed 156 cases, site incorrectly diagnosed 10 cases, cancer present but undiagnosed, 27 cases.

I have carried out a similar, executly planned study of 1 000 relevant hospital necropsies to ascertain the extent of diagnostic error in enneer drignosis as a whole and in the individual main groups of tumours. Although the series is smill, I can it least claim scrupidous care in the collection of the data and the highest possible accuracy in the necropsy diagnoses, all of which were verified or corrected by adequate microscopic examination. As will appear, this study provides indications not only of the degree of error to be expected in mortality and other strustics, but also of some import int statistical pitfalls.

THE ERRORS OF CANCER DIAGNOSIS REVEALED BY 1000 RELEVANT NECROPSIES

The investigation which was carried out at the Alfred Hospital Melbourne during the period July 1936 to December 1944 covered 1 000 consecutive necrop sies in which either a clinical diagnosis of malignant disease had been made or malignant disease was discovered post mortem. The necropsies were performed by me personally or under my personal supervision and the final diagnosis of every tumour was established histologically. Those few cases in which specific diagnosis of the nature of the tumour still remained uncertain after necropsy study were excluded from the series. Little or no selection of cases for necropsy was exercised during the period investigated necropsies were done on 58 per cent of all fatal cases in the Hospital (namely 3 000 necropsies in 5 163 deaths excluding coroner's cases) and there were very few fatal cancer cases which escaped necropsy. (The law regarding necropsy in Victoria is noteworthy in this respect. Necrops) may be performed on any person dying in a public hospital unless in objection has been lodged. Very few objections are lodged, so that necropsies are obtainable on nearly all cases. An enlightened law thus greatly fixours pathological research as compared with that of countries in which

necropsy cannot be obtained without the specific permission of the next-of kin)

Whenever possible the clinical diagnosis of each case was discussed with the resident doctor concerned before the necropsy was performed, and the diagnosis which would have been recorded on the death certificate in the absence of a necropsy was ascertained. During the greater part of the period concerned, it was the practice for the doctor to insert in the progress records of each patient a special note indicating the clinical diagnosis reached. In some cases in which this was not done and in which pre necropsy consultation was impracticable, the clinical diagnosis which would have been mide was nevertheless clear from the progress notes and the records of special investigations.

The clinical and necropsy diagnoses of any particular kind of primary tumour

X fell into the following 5 groups

A-clinical diagnosis of X, verified by necropsy

B—no malignant disease diagnosed clinically, λ disclosed by necropsy C—malignant disease diagnosed clinically, but primity site incorrect or

unspecified, X disclosed by necropsy

D-erroneous clinical diagnosis of V, some other primary tumour being

disclosed by necropsy

E—erroneous clinical diagnosis of λ , no malignant tumour of any kind being found at necropsy

Thus the total number of actual cases of X is the sum of A+B+C (B+C giving the total number of failures to diagnose X when it was present) The total number of clinical diagnoses of X is the sum of A+D+E (D+E being files positive diagnoses) The false total A+D+E, which shows the total number of death certificates which would have borne the diagnoses X if no necropsishad been performed can be compared with the actual number of cases of X, A+B+C. The main results of the investigation are set out in the accompanying Table I which will now be discussed

(1) General comments on the table

(a) The total diagnostic error

The 1000 necropsies comprised 943 actual cases of cancer and 57 eases which had been wrongly diagnosed clinically as cancer. Of the 943 actual cases 647 (69 per cent) had been diagnosed correctly, and 296 (31 per cent) had been mis diagnosed. (If any significance is to be attached to the total "amount of cancer' irrespective of site—which is very doubtful—then the total number of cases correctly diagnosed was 817 (A + C) which is 87 per cent of the true total while the total number of cases diagnosed clinically as "cancer, i.e. the total number of cancer death certificates which would have been recorded had no necropsies been performed, was 847 (A + C + E) which represents 92 per cent of the real number of cancer deaths. The findings thus suggest that the total number of cancer deaths recorded in mortality statistics may be only slightly less than the real (total).

(b) The statistical significance of positive and negative false diagnosis

For any given kind of turnour X failures to diagnose it when present (B + C) and false positive diagnoses of X will partly cancel each other and indeed may result in a mortality figure closely approximating to the real one i.e. A + D + E

may approximate to, or may equal, A+B+C For example, in the Table close approximation obtains for carcinomas of the stometh, panciers or ocso phagus. It is of the utmost importance, however, to recognize that the series of clinical diagnoses A+D+E even though its total may be nearly correct is a false basis for any further analyses of the properties of X, e.g. as regards age sex social or racial incidence clinical course or response to therapy. For not only does the series fail to include some real cases of X (B+C) but, far

TARKE

| | | | TABLE I | | | | | |
|---|-------------------|----------------------------------|---------|------------------------------|-----|----|-----|----------------|
| Character and Travellan | No of proven - | Correct clinical diagnosis | | Incorrect clinical diagnosis | | | | Ratio D + E |
| Clinical or post mortem diagnosis | | | | В | C D | | E | (approx) |
| | | No | 6/ | No | No | No | No | |
| Carcinoma of stomach - | 155 | 109 | 70 | 18 | 28 | 21 | 19 | 1 3 |
| Carcinoma of large intestine | 145 | 117 | 81 | 14 | 14 | 11 | `8 | 1 6 |
| Ghomas of brain | 83 | 74 | 89 | 8 | 1 | 9 | 3 | 16 |
| Carcinoma of lung | 71 | 43 | 61 | 13 | 15 | 4 | 5 | 1.5 |
| Lymphoid tumours | 57 | 38 | 67 | - 11 | 8 | | 1 | 1 38 |
| Carcinoma of breast - | 55 | 50 | 91 | 3 | 2 | 1 | | 1 50 |
| Carcinoma of gall bladder and ducts Carcinoma of kp oral cavity pharynx larynx | 46 | 10 | 22 | , 6 | 30 | 3 | 1 | 1 21 |
| salivary glands | 38 | 32 | 84 | ~~ | 6 | | | 0 |
| Caremoma of bladder - | 34 | 26 | 76 | 5 | 3 | 2 | | 1 13 |
| Careinoma of pancreas - | 33 | 11 | 33 | 8 | 14 | 21 | 4 | 2 1 |
| Carcinoma of prostate - | 31 | 25 | 81 | 5 | 1 | 3 | 4 | 1 31 |
| Careinoma of uterus - | 25 | 19 | 76 | | 4 | ā | ż | 1 3 |
| Careinoma of oesophagus | 20 | 13 | 65 | 2 | 4 | 4 | . 5 | 1 11 |
| Carcinoma of kidney - | 17 | 8 | 47 | 4 | 5 | i | 2 2 | 1 3 |
| Miscellaneous | 133 | 72 | 54 | 26 | 35 | 3 | 4 | 1 10 |
| TOTAL | 943 | 647 | 69 | 126 | 170 | 87 | 55 | 1 4) |

more important it wrongly includes a heterogeneous collection of cases of other diseases (D+E) differing from λ in their properties. These errors of inclusion (D+E) are more serious statistically than the errors of omusion (B+C) because they falsify the data in a positive way and to an unknown extent. Such positive falsification will be greatest in those groups of tumours in which the ratio D+E. A (given in the final column of the Table) is large e.g. in cartinoma of the panceas oesophagus or stomach. Thus in spite of hearly correct toatist (A+D+E) for these three tumours the clinical records uncorrected by the necropsy diagnoses would have been highly erroneous bases for any further malyses of their respective properties. On the other hand there were very few false positive diagnoses of carcinomas of the oral and neighbouring issues carcinoma of the bladder so that in spite of fallium to diagnose a proportion of actual cases in some of these groups analyses of the uncorrected elinical records of cases so diagnosed would have led to nearly correct results, since little positive

falsification was introduced. For the whole series, the ratio D + E A was 144 647. approximately 1 41, 1e for every 41 specifically correct diagnoses, there was one specifically incorrect

The total D. 87, does not enter into the total of 943 actual cancer cases, since it represents false clinical diagnoses of cases already included in group C a case of carcinoma of the stomach wrongly diagnosed clinically as carcinoma of the pinercas' is placed in group C as an actual case of careinoma of the stomach misdingnosed while the false diagnosis carcinoma of the panereas", which of course does not represent another actual case of cancer, is recorded in group D If the incorrect diagnoses arising out of group C had always specified the supposed primary site of the tumour, then the total for group D would have been equal to that of group C Actually, however, total C exceeds total D by 83, because there were 83 eases in which the clinician had displayed commendable caution in such diagnoses as 'abdominal malignancy", "malignancy of uncertain origin, disseminated careinoma intra thoracic tumour", etc. Had no necropsics been performed, these non committal diagnoses would have appeared on the death certificates, but they would not have introduced a positive source of error into subsequent statistical analyses of the properties of any given kind of tumour

That this series shows such a high proportion of non committal diagnoses of malignant disease-83 out of 943 actual cases (9 per cent)-is significant. This was due partly at least, to the wholesome caution engendered in the clinicians by the very knowledge that their diagnostic errors in fatal cancer cases would be exposed by necropsy Hence, instead of yielding to the natural inclination of all mankind "to give all things a name", they more often frankly admitted their uncertainties and the inconclusive nature of available evidence and seigntific eaution certainly does not obtain in the recording of death certificates in general general practitioners are often well content to enter their tentative diagnoses without indicating any element of uncertainty. Indeed, practitioners whose diagnostic errors are rarely or never exposed by necropsy (and these practi tioners are by far the majority) are themselves unaware of the frequency and extent of these errors Hence they commit themselves to positive false diagnoses much more often than the hospital elinician, whose whole training and close association with the pathologist necessarily inculcate greater scientific eaution Until it becomes a general practice for death certification to include a statement of the bases of dingnosis-according to the four grades of precision suggested above—and for published vital statistics regarding each kind of tumour to show the proportions of the diagnoses of each grade, we will be unable to assess the probable degree of positive error in these statistics. A main intention of the present analysis is to show how great these errors are likely to be

(c) The selected nature of the cases

The general question of the selected nature of hospital eases is discussed below Here we are concerned only with the evidence of such selection in the present series and some of the reasons for it. Selection is apparent from the relative frequencies of the various kinds of tumours in the series. While two notoriously common tumours gastrie and intestinal careinomas head the list, two other common ones mammary and uterine careinomas, are lower than we might have expected. The reasons for this art, related largely to the differences in duration and therapy of the respective diseases. The radical surgery of gastro intestinal carcinoma had a relatively high immediate post operative mortality, and many other inoperable cases were admitted to hospital as surgical or medical emergencies (intestinal obstruction severe haemorthage progressive anaemia etc.) and proved rapidly fatal. On the other hand, the immediate post operative or post radiational mortality of mammany or uterine cancer was small and many of the recurrent eases were transferred to the Austin Hospital for Chronic Diseases for treatment in the later stages. Thus many deaths from uterine and mammany carcinoma initially treated at the Affred Hospital did not take place in that Hospital. The fictitiously low figures for these two tumours in this series was not due to inequality in the numbers of males and females admitted to hospital during the period reviewed the Affred Hospital contained approximately equal numbers of male and female beds.

The high place occupied by glioma of the brain third on the list was due to the Alfred Hospital having had during the period reviewed the most netice neurosurgical clinie in Victoria—indeed in Austrahi—and to its chief, Mr H C Trumble having talen unusually keen interest in the pathological is well as the

clinical aspects of his cases

The series thus shows clearly, what Wells also has emphasized, that the relative frequencies of various tumours in the clinical and necropsy records of a general hospital are not the true relative frequencies but are influenced by many extraneous factors. These include differences in rate of progress and in prevaling methods of therapy for different kinds of tumours the proximity of a special enteer hospital or of other special hospital (or, conversely in neighbouring general hospital) of special clinics or of enthusiastic individual specialists. Many other selecting factors are noted where this subject is discussed again more generally below.

(2) Comments on particular tumours in the table

(a) Carcinoma of the stomach

Of 155 actual cases of this disease the clinicians had successfully diagnosed 70 per cent and had failed to diagnose 30 per cent. The ratio of positive mis diagnoses to correct diagnoses to correct diagnoses of carenoma of the stomach (D+EA) was high—more than 1.3. A series of cases showing such high proportions both of failures to diagnose and of erroneous inclusion of other diseases would clearly be vibuleless for any detailed analysis. Yet the total number of death certificates which would have been marked carenoma of the stomach' if no necropsies had been performed (A+D+F) closely approximates to the true number—149 instead of 155. The tumours responsible for most of the 21 false positive diagnoses of group D were extensions of the pancreas bility tract or oesophagus. Of the 19 non malignant cases which had been wrongly diagnosed as carenoma of the stomach. 10 were cases of chronic penticuleer.

(b) Caren oma of the large intestine

This has caused decidedly fewer diagnostic errors than careinoma of the stomach. Correct clinical diagnosts was attained in \$1 per cent of cases—and the ratio of file positive to correct diagnoses was less than 1 to 6. Of the 19

false positive diagnoses 11 were cases of neoplastic disease, in 6 cases carcinoma of the stomach

(c) Carcinoma of the biliary tract

A correct diagnosis was made in less than one quarter of the cases Of the 36 failures to diagnose this disease, in 18 the erroneous diagnosis had been "carcinoma of the pancreas" Non necropsy records of bihary encironma are clearly valueless stristic high.

(d) Caremema of the pancreas

Only one third of actual cases had been correctly diagnosed, and for every correct diagnosis there were 2 false positive diagnoses. Of the 25 false positive diagnoses. If were cases of carcinoma of the bile duets or gall bladder. If no incrops is had been done the number of deaths certified as due to "carcinoma of the pincrops (A + D + E) would have been close to the actual number—36 instead of 33 but two thirds of the cases so certified would not have been cases of pancrops are statistically useless

(e) Carcinomas of the cranio cervical passages

These had been correctly diagnosed in 84 per cent of cases and there were no false positive diagnoses. Two of the 6 failures to diagnose were due to large metastases in the cervical lymph glands from small symptomless primary growths in the tonsil and pharyax respectively.

(f) Carcinoma of the oesophagus

Two thirds of actual cases had been diagnosed correctly, the ratio of false positive to true diagnoses was 1 to 1½. Four of the 8 false positives were cases of carcinoma of the stomach.

(g) Carcinoma of the lung

Carcinoma of the lung had been correctly diagnosed in only 61 per cent of eases and the proportion of false positive to correct diagnoses (D+E,A) was 1 to 5. If no necropsies had been performed, the number of death certificates which would have borne the diagnosis 'circinoma of the lung would have been not more than 52 (A+D+E), 1e. 73 per cent of the actual number indeed the number would have been fewer than this because in several cases the clinician, relying mainly on radiographic reports would have committed himself to no more specific diagnosis than pulmonary neoplasm 'or even only 'intra thoracien neoplasm. All of the 15 misdiagnoses of group C had been due to clinically obtrusive secondary growths. These were in the brain in 4 cases and the clinical diagnoses had been 'cerebral tumour' in a fifth case (of group B) cerebral metastases had led to a clinical diagnosis of "confusional psychosis."

Study of an enlared series of 86 consecutive necropises on cases of pilmonary carcinoma—the above 71 cases and 13 additional order saves in a follow on gresults of Correct clinical diagnoses were recorded in 49 of 38 per of Timour was diagnosed series. The same of the s

(h) Carcinoma of the breast

Carcinoma of the breast had been diagnosed correctly in 91 per cent of the 55 cases, and there was only one case of false positive diagnosis. This series thus confirms the general opinion that clinical diagnoses are of such a degree of relia bility that they afford a valid basis for most statistical analyses of the properties of this disease.

(1) Carcinoma of the uterus

This had been correctly diagnosed in three quarters of the cases—falst positive diagnoses had been made in the proportion of 1 to 3. However salecting factors already referred to prevented this group from being a true sample of the disease, and gave a fictitiously high proportion of misdiagnoses. Many recurrent cases nearly all of proven nature were transferred in their later stages to the Austin Hospital for Chronic Diseases—while those dying in the Alfred Hospital included a disproportionate number of clinically unproven or unrecognized cases, and also of cases dying of post operative complications.

(1) Carcinoma of the hladder

Caremoma of the bladder had been correctly diagnosed in three quarters of the cases, and false positive diagnoses were infrequent

(k) Carcinoma of the prostate

Caremona of the prostate had been correctly diagnosed in four fifths of the cases but the proportion of false positive to true diagnoses was high—1 to 31

(I) Carcinoma of the kidney

This had been diagnosed correctly in less than one half of the cases and the proportion of false positive diagnoses was 1 in 3

(m) Gliomas of the brain

Gliomas of the brain were correctly diagnosed ante mortem in 89 per cent of cases. This relatively high degree of accuracy was due to the Hospital possessing as already mentioned a highly efficient neurosurgical chine and to the surgeon s usual practice of obtaining biopsy pieces for histo diagnosis of all brain tumours subjected to operation. On the other hand, the proportion of filse positive diagnoses of 'brain tumour (D + E A) was 1 in 6. Of the 12 false positive diagnoses. 8 were due to metastitie growths in the brain from unsuspected primary growths cliewhere. 4 of which were caremomas of the lung and the others included erreinome of the thirty of carenome of the kidness, and extinatous melanoma.

(n) Lymphoid tumours

Lymphoid tumours—comprising lymphatic leukaemia lymphosarcoma Hodgkin's diserve and reticulosarcom—had been diagnosed correctly in two thirds of the eases—and the number of false positive diagnoses was negligible (The same applied to micloi! kukaemia of which there were 10 actual cases all correctly diagnosed and one false diagnosis of ! leukaemia in a case of unsuspected gastric earcinoma with a leukaemoid reaction to metastatic deposits in bore marrow.)

(3) Conclusions on the series

About one third of 943 actual cancer cases had been misdiagnosed chincally In many of the particular groups of tumours the ratio of false positive to correct diagnoses was so great as to invalidate any statistical analyses which might have been attempted of the clinical records uncorrected by the necropsy findings This applied to carcinomas of the oesophagus stomach biliary tract pancreas lung prostite and kidney Fulures to diagnose a particular tumour-for most purposes statistically less serious than false positive diagnoses of that tumourwere so frequent in some groups as to render the clinical records (even including fal a positive diagnoses) of little value as an indication of the frequency of occur rence of the tumours in question this applied particularly to earcinomas of the ling bili try tract and kidney The tumours subject to fewest diagnostic errors were exemones of the breast eranio cervical region and intestines and gliomas of the brain but in the last named group, the high degree of diagnostic accuracy was due to a purely local factor namely the presence in the Hospital of a busy efficient neurosurgical unit. The diagnostic difficulties and errors frequently recorded in the histories of many of the cerebral tumour patients showed that outside such highly specialized clinics the diagnosis of this disease must be highly The series of cases of uterine carcinomas was too small and too selected to permit conclusions to be drawn but when allowance was made for the selecting factors it appeared probable that the diagnosis of this disease was fairly reliable

In what follows I shall try to show to what extent these conclusions are applicable to various kinds of statistical figures and problems

THE SELECTED NATURE OF HOSPITAL SAMPLES

As Wells pointed out hospital statistics are bound to be entirely musleading as to the frequency of cancer in different organs This is because hospital cases are subject to varying degrees of selection in many ways both recognized and unsuspected Some of the obvious selecting factors are the following-(1) the relative numbers of male and female beds and of adult and children's beds in the particular hospital (2) the presence in the hospital of special clinics or wards for or of individual clinicians particularly interested in, special classes of cases or, conversely the gynaecological neurological radiotherapeutic, etc presence of such special clinics or clinicians in neighbouring institutions, (3) the availability or otherwise of convalescent hospitals or after care homes to (4) the near presence which the general hospital passes its more chronic cases of a special cancer hospital or radiotherapeutic centre which will divert from the general hospital many cancer cases often of highly selected kinds, (5) the situation of the hospital determining whether it serves communities predominantly urban or rural industrial or residential and whether or not it receives a disproportionate number of patients employed in particular local industries such as chemical or mining These and other factors for which it is quite impracticable to make any quantitative allowances render hospital and other purely local statistics valueless as a basis for estimation of the relative frequencies of various tumours

However, in a large city hospital with approximately equal numbers of beds for adult males and females these factors will usually play little part in selecting e ises within most of the specific groups of common tumours. Thus 100 cases each of say, circinoma of the stomach carcinoma of the lung and ghom of the brain admitted to a general hospital even into special clinics, are likely to constitute nearly average samples of those diseases as they occur in the community generally and therefore to be valid material for analysis of the properties of those particular tumours. That they may not be absolutely representative samples however, is noted by Hill, patients admitted to hospital are on the average more seriously ill than those not admitted, so that our 100 cases of gastric carcinoma will be sicker and therefore less favourable for treatment than 100 non admitted cases of the same disease.

Post mortem cases may suffer selection in two special ways (a) In communities in which the law requires that special permission for necropsy shall be obtained in each case or in which necropsies are relatively infrequent for any other reason clearly there must be much selection of eases. In such communities in relatively few hospitals are more than 20 per cent of the deaths followed by post mortem examination, and the eases that are so examined are preponderatingly the eases that offered difficulty in diagnosis during life (Wells) Of course under these circum stances no accurate estimates of the frequency of diagnostic errors are possible (As I have already been eareful to point out this defect did not apply to my own series already analysed in which necropsies were done on 58 per cent of all fatal cases and very few fatal cancer cases escaped necropsy) (b) A less obvious but sometimes important kind of selection of necropsy cases depends on differences of duration modes of therapy and surgical risks in different classes of tumours. We had instances of this in mammary and uterine earemoma in the above series the transfer of many recurrent cases of both discases in their later stages to a special chronic hospital not only diminished the number coming to necropsy at the Alfred Hospital but in the case of uterine carcinoma led to some differentiation of cases according to the therapeutic results. Many groups of tumours are hable to such differentiation as regards eases coming to necropsy. Necropsies are likely to be obtained on cases dying in large general hospitals with adequate nathological departments i.e. on cases which succumb during radical surgical or other therapeutic procedures or those which have been retained in hospital because of metastatic or other special complications or because of diagnostic difficulties Necropsies are less likely to be obtained on cases of non-complicated recurrent disease of proven nature and of long duration many of which in their later stages are transferred from the general hospital to other institutions or are returned to their homes. Such differentiation of necropsy cases will obtain most for diseases like uterine, mammary and skin cancer in which diagnosis is usually straight forward and in which vigorous potentially curative surgical or radiational treatment is often undertaken in the early stages. It will obtain least for many kinds of internal cincer such as gastric biliary panerestic or pulmonary executomas which cause greater diagnostic difficulties are often speedily fatal, and are often not amenable to surgical or radiational attack. Hence a consecutive unselected series of general necropsies on cases of any of these usually hopeless susceral tumours is likely to be a fur average sample

The infrequency of post mortem examination in modern civilized communities is limentable. It is self-exident that for strustical and research purposes for prester numbers of necropsies should be performed. At present in most English

speaking communities less than 5 per cent of deaths are followed by necropsies, with the remaining 95 per cent vast amounts of valuable pathological material, as well as many unsuspected misdiagnoses from which the medical practitioner regrettably learns nothing, are bursed or burnt No greater service could be done for both the progress of pathological knowledge and the elevation of the standard of medical practice than the enactment of legislation permitting-or better requiring—the medical practitioner to obtain a competent necropsy (at the State expense) in every case of uncertain diagnosis, before signing the death certificate Were this to become a general practice, the sentimental antipathy of the public to necropsy (not really very strong even now) would soon disappear, intelligent doctors would welcome the opportunity of solving their diagnostic perplexities, observing the results of their treatment and learning from their mistakes, patho logical science would receive a great impetus, and soundly based mortality statistics would become possible 'We cannot have really reliable records until they are furnished by a large community in which for a period of several years all deaths are followed by post mortem examinations, and as yet there is not a community that has reached anything like this degree of enlightenment" (Wells)

HOW RELIABLE ARE CANCER MORTALITY STATISTICS ?

Mortality figures are bised on the diagnoses (and misdiagnoses) written on death certificates. These diagnoses vary widely in their reliability—from those mide from microscopically verified necropises to mere guesses made under the worst conditions of remote or busy general practices. Diagnoses of the lower grades of reliability certainly outnumber those of the higher. Hence, as already insisted on until death certificates are made to specify the basis of diagnosis, thereby permitting them to be classified into grades of reliability, the amount of error in mortality figures must remain unknown. Under present methods of death registration, we do not know and cannot find out how great the error in the vital statistics may be. We are sure that there is some error, it probably is large but no one knows how large it is. A pathologist who does necropises in many cases that have not been under the best hospital observation is likely to believe that the error is very large, and that conclusions of real value cannot be reached from the study of general mortality records. (Wells)

My studies outlined above not only endorse this opinion but permit particular conclusions regarding some of the main classes of tumours. These show that no relance can be placed on the mortality figures for carcinomas of the stomach oesophagus pancreas biliary tract and lung and that those for carcinomas of the kidney and of the prostite are of doubtful value. The mortality figures for carcinomas of the intesting of the facio cervical cavities are reliable, those for carcinomas of the intestine of the uterus and of the bladder, and for the tumours of lymphoid tissue are less accurate but are probably useful for most statistical purposes. The general mortality figures for cerebral tumours are almost certainly highly erroncous. These conclusions applicable to countries with the least fallacious mortality statistics such as Great Britain Australia. U.S.A. and the countries of pre war Western Europe are still more cogent for many other countries with lower general standards of medical and pathological practice.

such as those of the USSR the Balkans, South and Central America In these the mortality figures for all but the most obvious of external tumours, such as mammary and oral carcinomas, must be entirely unreliable For most Asiatic countries, of course no general mortility statistics exist

THE AGE STATISTICS OF TUMOURS

(1) Age distribution and age incidence

In any analysis of the age relationship of a series of cases of tumour, or of any other disease the age distribution and the age incidence of the disease must be clearly distinguished Age distribution states simply the numbers of cases falling in successive age periods in the series. Thus the age distribution of 1 060 proven necropsy cases of careinoma of all kinds which I have persontly examined was as shown in the horizontal column A of the following table.

| | | | TAE | ce tt | | | | | | |
|---|---|----|-----|-------|-----|-----|-----|-----|------|----|
| | Decades | 1 | 2 | 3 | 4 | 5 | 1 6 | 7 | 8 | 9 |
| Ā | No of cases in each decade - | 0 | ì | 12 | 32 | 130 | 253 | 345 | 239 | 48 |
| В | Percentage of cases in each decade | 0 | 0 | 1 | 3 | 12 | 24 | 33 | 22 5 | 45 |
| č | Percentage of total population in each decade (approx) - | 14 | 16 | 16 | 15 | 13 | 133 | ł 9 | 4 | 1 |
| D | Ratios B C | 0 | 0 | 0.00 | 810 | to | 2.2 | 37 | 56 | 45 |

The age distribution shown in columns A and B citt be expressed graphically as in Fig. 1 (a). If a sufficiently large series of cases were available and were graphed to show the numbers in each year of age a continuous smooth curve as in Fig. 1 (b) would be obtained.

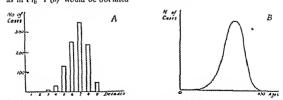


Fig. 1—(A) shows age distribution of carcinoma necropsies of Table II—(B) shows the smooth ideal curve of the age distribution of a large series

Such a graph of age distribution however takes no account of the age distribution of the whole population from which the carcinoma cases came. In order to discover the relative habilities of people of different ages to carcinoma we

Embryonic tumours 7 15, 169, 740-743 747-752 756-758, 806, 815-819 843-869 879-896

Embryological classification of tumours 14-15

Embryoma 976

P25-937
Enamel organ 308-310
Encapsulation of tumours 21 22
Encephaloid cancer 238
Enchondroms 670-671 674-676 710
Enchondrosis 670-671

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Enclayoma 321
Endogenous carcinoguns, $1 55 61 232, 435 439-440 597 937, 970
Endometriosis 535
Endometritis 534
Endothelioma 11 184-185 304 321 359, 462 530 643, 645-647 686-687 693 696 702 718,
      761 778
Endothelium meaning of 11 645-646
Enzymes in tumours 137 143
Eosmophil leucocytes and eosmophilia with tumours 139, 530 771-777 795
Ependymal spongioblastoma 803 804, 805
Ependymoblastoma, 802 803 814
Ependy moma 185 803, 806 814-815 818
Ephebogenesis 976
Epidermis (see Skin)
Epididymis carcinoma of 579-580
      cysts of 580
      experimental tumour of 39
      lymphangioms of 579 711
      rhabdomyosarcoma of 751
      secondary tumours of 465
      teratoma of 573 943 948
Engnaths 952-953
Epiphyses tumours of 678 682
Epithelial cavities, invaded by tumours 162-163 531
       metastasis by implantation in 186-189
Epithelioma 269
Epithelium meaning of 11
Eponyms inappropriate 774-775
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 Ergot, 841
 Erythraemia 797-799
 Erythroblastoma 797~799
 Erythroblastosis foetalis 794
 Erythrocythaemia 797-799
 Erythroleukaemia 795
 Erythroplasia 287 290 597
 Ethyl-cholanthrene 33
 Eustachian tube carcinoma of 300
       invaded by tumours 162
       rhabdomyosarcoma of 741
 Ewing s tumour of bone 686-687 858 865-868
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       animals and carcinogenic agents)
       cumulative effects in 42
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       precancerous changes in 40-42
                                           [12]
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Dermatofibroma 650
Dermoid cysts 944 (see also Teratomata)
Desmoid tumour 650-651
Desmoplasia 136
Desoxycholic acid 32 33 34 61 435
Diabetes associated with cancer 197 448
Diagnosis chemical tests in 145
      difficulties and errors of 67-76 171-172 184-185 204 243 244 245 298 301 304
            359-360 371-376 408-410 437 440-441 443 447-449 462-465 482-485 587
            590-591 610-612 617 627 669-670 702-703 761 776 784-786 840 844 864-
            868 907-909 912 915
      improvements in 85 360 391-392
Diamino-dinaphthyl 44 46
Diaphyseal aclasis 671-672
Dibenzacridine 32 34 35
Dihenzanthracene 3 32-44 48
Dibenzcarbazole 32 34 39 44 46
Dibenzfluorene 32 34
Dibenzypyrene 34
Diktyoma 895-896
 Dimethylaminoazobenzene 44-46
 Dimethyl benzanthracene 32 33 35 36
 Distosomiasis 434
 Dog experimental tumours in 30 31 46
       Hodgkin's disease in 780
       spontaneous turnours in 94-95 117 119 140 211-213 221 226 263 264-265 306
            323 361-362 393 420-421 432-433 439 445 457 470 510-512 524 548 552
            555 562-564 579 580 586 597 604 612-613 630 634 639 654-655 666 689-690
            713 780-781 796 799-800 820 841 874
 Dopa test 904 911
 Duck transfer of fowl tumour to 100
 Duodenum adenoma of 413
       carcinoma of 412 413
       invaded by gastric carcinoma 157 404 406
       leiomyoma of 734
       polypi of 412-413
       secondary tumours of 991
       ulcer associated with carcinoma of 413
 Dural sinuses invaded by turnours 683 721 726-727
 Dura mater chloroma of 797
       endothelioma of 718
       secondary tumours of 178 242 245 431 797-799
  Duration of tumours 82-83
  Dusts possibly carcinogenic 54 363
  Dyschondroplasia 671
  Dystrophia adiposo-senitalis 628 630 658
  Ear carcinoma of 30 47 55 56 109
        neurilemmoma of 841
        secondary tumours of 464 683
  Ecchondroma 675-677
  Ecchondrosis 918
  Ecchordosis 918-919
  Ehrlich mouse carcinoma 100
  Emboli and embolism from tumours
        abortive 175 178-180 206
        in blood vessels 172-177 430 436 672 732 749
        in lymph vessels 166-171
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Kidney (cont.)
      carcinoma of (cont.)
            proknosis of 459 461
            race incidence of 457
            sex incidence of 81 457
            site of 457
            structure of 458-462
            veins invaded by 158 159, 459
      careino sarcoma of 461
      embryonic tumours of 96 97 101 120, 925 912
      in myelomatosis 788
      leiomyoma of 453 736
      hooms of 457
      lymphangioma of 711
      mixed tumours of, 461 756 925-932
      nephroblastoma of 925-932
      osteosarcoma of 689
      rhabdomy osarcoma of 756
      sarcoma of 461 689
      sclerosis of preceding tumours 454 457
      secondary tumours of 178 242, 303 410 426 430 431 463 477 770 797-799 919 991
      teratoms of 931
      tumour-embale in 176
Kidney pelvis, Brunn s nests in 471-472
      calculi in 472 640
      carcinoma of 38 46 81 168 188 189 467-477
      implantation of tumours in 189
      leucoplakia of 468 471-472
      metaplasia of 471-472
      papilloma of 467-477
      nychtis of 471-472
      secondary tumours of 189
Kraurosis 287 290, 549
Krukenberg s tumour 405 408-409 425 492
Kultschitzky celis 414-415
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must compare the percentages of the cases in the successive age periods with the percentages of the general population in those same age periods. Let us assume—as figures given by Crockett (1943) show, the assumption will be nearly correct—that in the population from which the foregoing carcinoma cases came the percentage of people in the successive decades were the same as those in England and Wales in 1938 which are given approximately in the horizontal column C. The column D gives the successive ratios B C, which express the relative liabilities of people of different ages to develop carcinoma. It will be seen that the incidence of fatal carcinoma rises steeply and continuously into old age (the figures for the ninth decade are unreliable because the number of cases is too small)

As another example of the important distinction between age distribution and age incidence of tumours, Lane Claypon's figures regarding carcinoma of the breast may be cited. Analysis of 4,301 surgical cases (1924) showed the following percentages of cases in successive decades

| TABLE III | | | | | | | | | | | | | |
|--------------|------|-----|---|---|---|---|----|------|------|------|------|-----|----|
| Decade - | | - | - | - | - | - | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Percentage o | f ca | ses | - | | - | - | 18 | 15 5 | 35 5 | 28 2 | 15 1 | 3 3 | 06 |

But a curve of the mortality rates for mammary cancer per 1,000 of female popula tion living in successive age periods (1928) shows a continuous rise from youth to old age. The same is shown in Table IV.

TABLE IV

AGE AND BREAST CANCER US REGISTRATION STATES 1930

(From Bogen 1935)

| Ages | Population | Deaths from breast cancer | Rates per 100 000 | Percentages o total | |
|----------|-------------|---------------------------|----------------------|---------------------|--|
| 0-14 | 34 180 745 | 5 | 0.01 | | |
| 15-24 | 21 235 387 | 21 | 0 10 | 0.20 | |
| 25-34 | 18 017 199 | 290 | 1 61 | 2 68 | |
| 35-44 | 16 451 562 | 1 441 | 8 76 | 13 32 | |
| 45-54 | 12 487 707 | 2 671 | 21 42 | 24 68 | |
| 55-64 | 8 086 614 | 2 935 | 36 30 | 27 10 | |
| 65-74 | 4 559 756 | 2 107 | 46 20 | 19 44 | |
| Over 75 | 1 841 550 | 1 354 | 73 60 | 12 50 | |
| All ages | 116 950 331 | 10 831 | 9 27 | 100 | |

In mortality statistics, the age incidences of tumours are conveniently expressed, as IT able IV in mortality rates per 100 000 of persons living in the respective age periods. But in non mortality statistics, ratios as in Table II must be used to assess relative liabilities to particular tumours at various ages

(2) Modal and mean ages

The peak of the curve in Fig 1 shows the modal age (i e the most frequent age) of death from carcinoma in the series considered. This is not the same as

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the average or mean age but in most homogeneous groups of tumours the mean and modal ages do not differ by more than 3 or 4 years

Different kinds of tumours of course differ very greatly in their age incidence and even different kinds of carcinomas show decidedly different mean ages. Thus in the series of Table II, the mean ages at death of particular groups were is follows

TABLE V

| | , | 2201 | nomas | | | 1 | | Mean ages | | | |
|------------|------------|--------|--------|-----|-----|-----|-----|-----------|-------|----------|--|
| | Catemonias | | | | | | M | F | Total | in years | |
| Lung- | _ | _ | ~ | | - | - 1 | 70 | 14 | 84 | 55.4 | |
| Cervix ute | T1 | | ~ | ~ | - | ~ 1 | _ | 37 | 37 | 56 2 | |
| Ovary | - | - | - | | - | (| | 18 | 18 | 567 | |
| Lidney | - | - | - | | *** | | 23 | 4 | 1 27 | 57.7 | |
| Breast | ~ | - | ~ | ~ | | | _ | 92 | 92 | 58 1 | |
| Renal pel | vis an | d ure | ter | | - | - | 7 | 1 | 1 8 | 60 1 | |
| Large into | | - | - | | - | ~ | 114 | 76 | 190 | 60 5 | |
| Corpus ut | | - | ~ | - | - | ~ | | 12 | 12 | 611 | |
| Larynx | _ | - | ~ | ~ | | ~ | 10 | 1 | 11 | 62.2 | |
| Stomach | ~ | ~ | - | | - | ~ | 157 | 70 | 227 | 1 62 3 | |
| Bile ducts | and : | gall b | ladder | - | | | 25 | 33 | 58 | 63 6 | |
| Buccai car | | | | | - | _ | 61 | 14 | 75 | 63.9 | |
| Bladder | ź | ~ | - | | - | | 27 | 10 | 37 | 643 | |
| Pancreas | ~ | | - | *** | | | 28 | 14 | 43 | 64.8 | |
| Octophia | us | - | - | - | | | 32 | 3 | 35 | 66 7 | |
| Prostate | ~ | - | ~ | | | | 40 | | 40 | 718 | |
| Sundry | - | - | _ | - | - | t | 41 | 26 | 67 | 63 5 | |
| Τσ | TALS | - | - | - | | | 635 | 425 | 1 060 | 620 | |

The order of the tumours in Table V is closely similar to that of most other reported series of fatal exemomas though the actual mean ages for particular tumours differ from series to series according to the age composition of the respective communities Carcinomas of the lung cervix ovary kidney and breast occur at and kill at mean ages decidedly less than that of carcinoms in general. while careinomis of the bladder, pancreas oesophagus and particularly of the prostate occur and kill at average ages later than the general mean. A similar order of tumours obtains also in many reported series of non fatal clinical cases the recorded ares of which are those of onset of symptoms or of diagnosis. Thus the large series of New York cases reported by Pack and Le Fevre shows the mean ages of renal cervical uterine, mammary and pulmonary carcinomas to be decidedly less than, and the mean ages of oesophageal cervical and prostatic careinomas to be decidedly greater than the average of all careinoma cases In Pack's and Le Fevre's series however the mean ages throughout are several years less than in those of Table V partly because of the younger mean are of their population partly because of the difference between chincally recorded ages and ages at death. This last matter requires further discussion

(3) Ages of onset, of diagnosis and of death duration of tumours

The age of onset of most internal tumours cannot be determined. Not only are the first symptoms of many tumours insidious in onset, but the tumours are often already of long duration when the first symptoms appear Indeed, it is for from unusual for primary growths to remain symptomless throughout their course producing their first signs by their metastases or being discovered unex pectedly at necropsy. The tumours most prone to do this include many carcinomas of the lung kidney and stomach but all main classes of internal carcinomas afford similar instances. Although teratomis clearly take origin in early embryonic or foctal life, their clinical appearance is usually deferred for varying periods from childhood to old age, or they may be discovered only incidentally at necropsy So also neuroblastoms and ganglioneuroms, nephroblastoms and other embryonic tumours, though arising in early developmental life, may not become clinically apparent until later childhood or adolescence. Many internal benign tumours, c.g. uterine myomas, remain symptomicss and unsuspected for long periods Clearly for all such tumours as the foregoing, the real mean ages of onset of the neoplastic changes cannot be deduced even approximately from the ages of symptomatic onset. The ages of onset of externally visible or palpable growths, or of those whose position is such that they usually occasion early symptoms, can be more recurricly assessed. This applies to most carcinomas of the skin, breast buccal eavity, oesophagus pylorus bile duets and uterus and to many intraeranial tumours. But plentiful exceptions occur even carei nomas of the breast are often quite large and clearly of considerable age when they are first noticed

Age at diagnosis, or at admission to hospital which is given in many clinical series of cases clearly lacks precision. It depends arbitrarily on the very variable lag period between onset of first symptoms and the patient's seeking medical aid on the diagnostic difficulties of the case and on the efficiency of the clinicians concerned. And as we have seen carlier in this Chapter in many classes of internal tumours many misdrignoses are made by the most competent clinicians.

Age at death—the age recorded in necropsy and mortality statistics, is precise and definite. But in the latter, of course the value of the age records as of all other recorded details is limited by the degree of diagnostic error in the class of tumours considered, especially by the proportion of positive misdiagnoses erroneously included in that class. The ages it death of necropsy cases of proven nature are then the only absolutely definite and reliable age records in cancer.

The natural duration of tumours is for reasons already given often impossible to assess. Greenwood estimated the mean symptomatic durations in months of untreated carcinoma cases to be—for the breast 38.3 rectum 26.7, uterus 20.9 stomach 16.8 tongue and mouth 16.5, and oesophagus 12.0 But he was careful to point out that the precise times of onset of cancerous changes were unknown and that the probable order of reliability of the dates of symptomatic onset in this respect was—tongue, breast uterus, rectum, oesophagus, stomach. The effect of treatment on duration, and therefore on final menn age, was exemplified



mortality statistics, they can be valid only between countries with similar standards of practice and registration. Most of the countries of Western Europe, of the Inglish speaking parts of the British Empire and USA are probably of nearly equal standards so that their mortality figures may be broadly comparable Clearly, however, no two countries can be exactly comparable in this respect and the ways in which their standards diverge and the extent to which they diverge are unknown. Bashford lone ago doubted the reliability of comparisons of the mortality figures of even the European countries and Hill in 1939 described comparisons of the mortality figures of different countries as "fundamentally of a dubious character." Between countries of widely different standards of medical practice and registration comparisons of tumour incidence as recorded in mortality figures must be quite unreliable, except perhaps as regards the most obvious kinds of external growths such as mammary and oral carcinomas For this reason comparisons between the countries just mentioned, on the one hand, and those of Eastern Europe, the USSR. Asia and S America, on the other, must be viewed with great caution

As regards (b), we have seen that in modern envilved communities more than half of the cancer deaths occur at ages over 60 and more than a quarter of them to ages over 70. Clearly then communities differing only moderately in age distribution, especially as regards the proportion of persons in the later decades will differ very decidedly in tumour incidence. Young recently established communities, with relatively few old people will suffer from far less cancer than an old settled community with a high proportion of old people. Native communities with relatively low mean expectation of life, such as most of those of Asia, Africa and the Pacific will have relatively low encer incidence. No valid comparisons of tumour incidence between different mees, nations or other aggregates of people can be made unless their respective age compositions are known. These are known for most civilized communities of European origin, but not for the native communities referred to.

It is necessary to refer here to a hoary fallacy which though repeatedly exposed by Bashford, Wells, Cramer and others, is still voiced—namely, that 'cancer is a disease of eavilization" or that "cancer is rare in savage races". Since savage races have neither mortality statistics nor age composition statistics, comparison of the frequency of cancer in them with that in enalized races earned be made. Moreover ample pathological and hospital records exist to show that tumours of all kinds do occur in all known races that many of the kinds of tumours which are commonest with us are also common in native races, and that some tumours which are relatively infrequent with us are common in certain native races. The following recent papers are valuable sources of information regarding tumours in natives of India and Ceylon—Nath and Grewal (1935, 1937 and 1939), khanolkar (1945) and Cooray (1944), of the East Indies—Bonne (1935), of China—Bercovitz (1941), of the West Indies—Hartz (1940), of Nigeria—Simith and Elmes (1934) of South Africa—Strachan (1934) and of Negroes in America—Quinland and Cuff (1940). Other references to particular tumours are given in the Chapters of Part II

Comparison of the mortality figures of various countries which possess reliable data shows that racial differences of susceptibility to cancer generally,

as follows the expectation of life of a healthy woman 55 years old was 18 87 years, of a woman of 55 with untreated breast cancer 3 25 years, of a woman with breast cancer operated on under average conditions 5 74 years, and under the best conditions (with localized carcinoma and no involvement of lymph glands) 12 93 years

Comment

Briefly then, ages of symptomatic onset and ages of diagnosis are indefinite figures which give only rough indications of the real ages of onset of tumours. Ages at death are definite figures, but the differences between them and the corresponding ages of onset vary greatly according to the natural durations of the tumours, their productivity of symptoms and the efficacy of treatment. These considerations though obvoice enough are often overlooked in published papers. Any statistics dealing with age meidence should make clear what agus are referred to, should ensure that these are homogeneous in kind throughout the series and should indicate whether or not treatment may have affected the duration of the tumours.

(4) The canter age

To what extent cancer is predominantly a disease of the elderly can be seen in Table II. This shows that people over 70 years old (5 per cent of the population) account for 27 per cent of fatil careinomas people over 60 (14 per cent of the population) for 60 per cent, and people over 50 (38 per cent of the population) for 84 per cent. I e about four fifths of all fatal careinomas occur in the oldest one third of the community. This accords with the Registrar General's figures for cancer deaths in England and Wales in 1938, which show that nearly one hiff of the 68 600 cancer deaths were at ages over 65 years and about two thirds of them it ages over 60 years. We now know that cancer is mainly a disease of the elderly, not because senile tissues are predisposed to cancer, as was once supposed but because of the usually long latent periods elapsing between the application of circinogenic stimult and the development of tumours. Occupitional ind experimental tumours show that these periods often occupy large fractions of the life spans of the affected animals. The rapidly increasing liability to cancer with advancing age is of the utmost importance in comparing the incidence of tumours in different races, countries or communities, and in estimating the trends of tumour incidence with the passage of time in the same community.

NATIONAL AND RACIAL DIFFERENCES OF TUMOUR INCIDENCE

In comparing the incidence of tumours in general or of particular kinds of tumours in two different peoples two preliminary questions already indicated must be asked (a) Are their respective statistics comparable in reliability? and (b) Are their respective populations similar in age composition?

As regards (a) we have already seen that even the best mortality statistics are unreliable for most internal cancers and that the degree of unreliability must vary from community to community according to the standards of medical practice. Since most companisons between different countries are made from their

trends in males and females, mentioned in paragraph (b) above—over 90 per cent of male cancers are internal and difficult to diagnose while 40 per cent of female cancers are accessible and casy to diagnose—Duffield and Di Mario concluded that much if not all, of the apparent increase in cancer mortality has resulted directly from improved diagnostic techniques and the increased opportunities for their use.

- (d) Efficiency of treatment must also influence, to an unknown extent, the apparent trends of cancer morthlity. Improved surgical and radiational therapy must surely have caused some progressive reduction in the proportion of fatal cancer cases and to that extent must have masked the real incidence and trend of cancer. Suppose that some highly efficacious method of treatment were to be introduced, then it would be possible for the real incidence of cancer to be increasing and yet for the mortality rates to show a sharp downward trend
- (c) Efficiency of prophylavis against infective diseases is important in modifying the incidence and trend of neoplastic diseases. Decreased deaths from typhoid fever pneumonia tuberculosis and other preventable diseases mean a corresponding increase in deaths from "non preventable diseases such as cardiovascular and rend disease and cancer. From Canadian figures, Macklin (1932) concluded that cancer was increasing, especially in age groups over 60. "Excellent public health measures and high cancer rates are inseparable, at least for the present. Those who point to the low cancer rates existing among primitive peoples, and who state that cancer is a disease of modern civilization, neglect to call attention to the fact that preventive medicine is itself a triumph of modern civilization."

Conclusion

There is no evidence that the real incidence of cancer as a whole is changing save in so far as the age compositions of populations change, or as people are prevented from dying of other diseases. Hoffman and others who have believed that there has been a real and alarming increase of cancer in all eivilized countries, have underrated the great degree of fallibility in the registered causes of death and the degree of improvement effected in these by improved methods of diagnosis.

(2) Trends of incidence of particular tumours

The foregoing discussion of the trend of cancer as a whole has focused attention on the various factors which must be weighed in considering the trend of any disease or group of disease. It is doubtful, however, whether the trend of so wague a disease as cancer as a whole is worth ascertaining. Much more important is it to ascertain whether particular kinds of tumours show distinct trends. Clearly, for reasons already stated it is at present useless to attempt to discover the trends of any of the internal cancers the diagnosis of many of which is erroneous. But of such tumours as carcinomas of the buccal cavity skin, breast and uterus there can have been but little improvement in diagnosis during recent decades, and comparison of their present mortality rates with those of earlier periods is legitimate. This shows that in both Great Britain and U.S.A. of recent years, there has been a real increase of breast carcinoma, there has probably been a real decrease of carcinoma of the uterus, and that there

if such exist are slight. The age standardized cancer rates of different countries are closely similar. The relative frequencies with which the various sites are affected vary from country to country clearly because of differences of exposure to external carcinogenic stimuli resulting from peculiarities of custom, habit and occupation

TRENDS IN TUMOUR INCIDENCE

It is pertinent to ask whether in a given community the incidence of cancer ' as a whole or of particular kinds of tumours has altered demonstrably with the passage of time. Let us clarify the several factors involved in answering the following familiar question.

(I) Is cancer mereasing?

- (a) The figures used in the attempt to answer this question are usually the mortality rites as estimated from death certificates in successive periods. We have already seen that these are subject to great error as regards nearly all kinds of internal tumours and that the aggregated figures for all kinds of malignant disease irrespective of errors of diagnosis of site are less than the real figures Just how great this margin of aggregate error is or to what extent it may vary from period to period with improved methods of diagnosis and registration, we do not know
- (b) Alterations in the are composition of the community during the successive periods considered must be known and allowed for. If a population is ageing 1 e showing increasing proportions of old people with the passage of time, then clearly cancer will be increasing in it. But this increase will be of little interest it is only age standardized trends which are of real significance. To what extent the age standardized figures correct the impression given by the crude mortality figures is shown in the Registrar General's report for 1932, cited by Cramer. In that year the crude figures showed an increase of cancer mortality over that of the decennal period 1901 10 of no less than 93 per cent for males and 48 per cent for females, but correction for the change in age-composition of the population reduced these figures to 34 per cent respectively.
- (c) Improvements in diagnosis and registration clearly have an important effect on cancer mortality records and their apparent trends. It is only within recent years that many radiographic, endoscopic, biochemical and pathological methods of diagnosis have been introduced or perfected, and that adventurous surgery has explored regions and diseases formerly regarded as beyond her bounds. All this has greatly improved and is still improving cancer diagnosis but no one can assess the exact degree of improvement. Many writers, e.g. Cramer Dublin Duffield and Di Mario have noted that the increase in age standardized cancer death rates during the last few decades has been mainly for cancer of internal sites and that there has been relatively little increase in rates for accessible easily diagnosed tumours. This difference strongly suggests that the increased rates for internal cancers are largely due to improved diagnosis. As Duffield and Di Mario pointed out this also explains the difference of the apparent cancer

contains much detailed evidence regarding differences of mortality rates from various kinds of cancer according to social class. The comparisons were made by issigning each occupation to one or other of five descending social classes and issessing the standardized mortality ratio (SMR) of each kind of cancer in each of the five classes. The SMR was estimated as a percentage ratio of the actual number of deaths in the particular class to the calculated standard number for the class estimated from its known age and sex composition. It is a measure of the relative liability of comparable samples of the classes to the particular tumour.

It was found that for cancers of the upper alimentary canal from mouth to pylorus the SMR s for males of the five descending social classes were 63, 80 97 109 and 129. When married women were grouped according to the social class of their husbands, they showed a similar class gradient for upper alimentary cancers. The factors responsible for the class gradient in cancer of the buccal cavity ocsophagus and stomach, are therefore almost as effective in the aggregate immongst waves of men engaged in the various occupations forming the social classes as amongst men actually engaged in the occupations, and it must be concluded that these factors are connected to a greater degree with the general economic circumstances home life or dictaries which are associated with occupations than with the occupations themselves

'Other sites which manifest an unmistakable social class gradient amongst males, tending to maximal levels amongst the unskilled classes, are the largny skin scrotum and penis, which are sites exposed to external irritants. The mortality ratio for the largny ranged from 60 for males of Class I to 143 for males of Class V, but it is significant that married women showed no significant social class gradient, thus suggesting that the factors responsible for the excess of cancer of this site amongst unskilled males are directly associated with occupation. For cancer of the skin on the other hand married women showed a similar class gradient to males, showing that peculiarities of occupation are by no means the only factors concerned.'

Ulterine cancer showed a class gradient from S M R of 65 for married women in Class I to 130 in Class V. Uterine cancer in single women, and vulval and vaginal cancer also showed a similar, but less pronounced, gradient. Cancer of the breast diminished from the higher to the lower classes (138–116, 103–84 and 82), so did cancer of the ovary (143, 116–102–77, 83). For single women, the class gradient for breast cancer was much less marked than for married women

Cancer of the buccal cavity and pharynx showed a pronounced class gradient for males, the lower classes suffering most but a less distinct gradient for females "Ether the type of occupation in itself or certain habits which are greatly influenced by social class amongst men but not amongst women must be important factors in the production of cancer of the buccal cavity and pharynx in the men Cancers of the stomach and ocsophagus showed pronounced class gradients in both men and women the lower classes suffering most Cancers of the intestine and of the bladder showed no significant class differences

While the social gradients for accessible easily diagnosed tumours such as those of the breast, uterus skin, and buccal cavity may be accepted without reserve the large degree of error known to be present in the mortality records

has probably been little or no change in the incidence of carcinomas of the skin or buccal cavity (Cramer Duffield and Di Mario Bogen)

OCCUPATION AND CANCER

The association of particular kinds of tumours with certain occupations is some times too obvious to require statistical analysis e.g. chimney sweep s cancer cotton spinner's cancer analyne cancer of the bladder carcinoma of the lung in the miners of Schneeberg and Joachimsthal and osteosarcomis in the dial painters of New Jersey.

However, apart from immediately obvious occupational associations of this kind statistical analysis shows significant occupational differences in the incidence of particular tumours or of cancer generally Thus the Registrar General s report on cancer deaths in England and Wales for 1930 32 showed general rates much higher than the average for furriers glass blowers tin and copper miners stevedores curriers leather dressers etc. and rates much lower than the average for teachers clergymen retailers telephonists etc. Or as an example of occupa tional differences of a particular kind of tumour the mortality rates from cancer of the buccal cavity and pharynx were much higher than the average in barmen furnacemen, dock labourers, horse drivers general labourers hotel keeners etc and much lower than the average in retailers elergymen, tram drivers rulway officials agents and brokers teachers bank officials civil servants farmers Although these differences are statistically significant the occupational factors responsible for them are uncertain occupations are often difficult to classify with precision people change their occupations and as regards tumour causation occupation earlier in life is more important than that engaged in later and recorded on a death certificate

However, the many occupational differences revealed by analyses such as the Registrar General's afford hints of possible carcinogenie factors which are worth further statistical and experimental investigation. It is important to emphasize here the great length of the latent period often intervening between the application of the careinogenic stimulus and the eventual appearance of the tumour. This makes it useless to look for the causes of human tumours in the occupations and habits of affected persons during the parts of their lives imme diately preceding the appearance of their tumours. The tumour of to day is often the consequence of stimuli applied 10 20 or 40 years ago. Our medical histories and therefore our statistical data of tumour patients are often totally deficient in this respect detailed inquiry into the occupations and hibits of the whole of the patient's previous life remote as well as recent as rarely undertaken. Here is a great almost virgin field of research exploration of which by competent workers with a full knowledge of the problems involved must be undertaken if we are to sift out of our complex environment the carcinogenic factors which are yet unrecognized And the same applies to the educidation of the causes of many other chronic diseases—blood disease

SOCIAL CLASS AND CANCER

The Registrar General's report dealing with occupational mortality for 1930-32

which shows the unexpected frequency with which multiple cases of cancer may occur in families of various sizes without there being any hereditary tendency. "Usually, too only one part of the field is reported in medical literature, for notice is taken of the remarkable instances and no reference made to the cases in which no inheritance is apparent." (Hill)

One important statistical approach to the question of familial or inherited susceptibility to cancer of a given organ is to ascertain whether the immediate relatives of victims of the disease show it with greater frequency than the general population of comparable ages Detailed studies of this kind, carried out by Wassink in Holland and Waaler in Norway, and summarized by Cramer (1938 and 1942) and by Blank (1944) appeared to show that carcinoma of the breast, uterus and prostate did occur with abnormal family frequency. Thus close female relatives of victims of breast cancer showed a decidedly higher incidence of breast cancer than could be accounted for by chance, but this did not apply to cancer of other organs while the close semale relatives of sufferers from uterine circinonia showed an abnormally high incidence of uterine carcinoma Carcinoma of the stomach showed a slight familial predisposition, but no pre disposition was apparent with carcinomas of the skin or hip. Before drawing final conclusions from studies of this kind, further careful investigation is needed, and it must not be forgotten that near relatives are often exposed to similar environments

Another method of examining the possible influence of heredity in human tumours is to ascertain the tumour incidence in identical twins. Great caution is needed, however in collecting and evaluating such information adequately authenticated cases are few, and instances of the occurrence of similar tumours in twins are much more likely to be reported than instances of non concurrence Failure to appreciate this misled McFarland and Meade into concluding that tumors occurring in homologous twins seem always to be similar, sym Versluys however, critically examining this metrical and simultaneous question, found that the occurrence of a tumour in one twin only was more frequent than concurrent tumours in both twins, and that dissimilar tumours in twins were commoner than similar ones whence he concluded that evogenous factors were more important than genetic factors in the genesis of tumours in Westz also adduced evidence that concordant cancer in identical twins is exceptional Of course, with dise uses of known familial character, such as retinoblastoma, polyposis and xeroderma monozygotic twins are very likely to develop similar simultaneous tumours, but with these special exceptions, the pathology of twins gives little evidence of any strong genetic predisposition to cancer

Kennaway and Kennaway discussing (a) the total incidence and (b) the incubation period of particular kinds of cancer in man, point out that more intense carcinogenic stimuli are required to shorten (b) than to increase (a), and that (b) particularly is influenced by genetic factors. Thus the mean age at death from chimney sweep's scrotal cancer a disease probably due wholly to external carcinogens and devoid of any genetic predisposition, is about the same as it is in the general population although the liability to this disease among sweeps is enormously greater than in most other occupations. But forms of cancer in which a familial factor is concerned (familial polyposis, xeroderma pigmentosum,

of gastrie, ovarian, and many other visceral tumours, should engender caution in accepting the apparent social gradients for these

SEX AND CANCER

Apart from the organs of reproduction and the breast many other organs show pronounced sex differences of tumour incidence. These will be discussed in the Chapters of Part II, only a few examples will be given here.

The Registrar General's report 1930 32 contains the following figures

TABLE VI

| | | c | of can | | | | | | Des | iths |
|-------------|-------|------|--------|-------|----|---|---|---|--------|---------|
| | | 2166 | ot can | cinom | ia | | | | Males | Females |
| Lip | | | _ | | | | - | _ | 849 | 20 |
| Tongue - | - | _ | - | _ | - | | - | - | 3 225 | 217 |
| Mouth and t | onsil | _ | | | - | - | ~ | | 1 706 | 143 |
| Pharyny ~ | - | ~ | _ | - | | - | - | - | 1 075 | 221 |
| Stomach - | _ | - | - | - | ~ | - | - | - | 18 976 | 9 243 |
| Bladder - | _ | ~ | _ | _ | _ | ~ | - | - | 2 668 | 675 |

The preponderance of males in each of these groups of tumours was even more than shown because the population contained an excess of females

Mortality figures are too unreliable for assessing the sex ratio of most kinds of internal cancers these are better estimated from large series of proced clinical or necrops, cases, such as my series of Table V above. Since this series was from a hospital which contained approximately equal numbers of male and female beds, the ratios shown may be taken is approximate measures of the relative liabilities of men and women to the diseases in question. It will be seen that Tables V and VI show roughly similar sex ratios for the tumours listed in both Lymphosarcoma, leukaemias and Hodgkin's disease also show a pronounced preponderance in mike (see Chapter 49). Notice that nearly all kinds of malignant tumours of viscera other than the reproductive are commoner in men than in women. Yet the total number of finale deaths from cancer exceeds the total number of male deaths. In England and Wales in 1938, the finale and male detths from malignant disease were recorded as 35.913 and 32.692 respectively. This is because of the much greater frequency of uterine and mammary cancer than of cancer of the male reproductive organs.

HEREDITY AND CANCER

The inheritance of a predisposition to exneer is obvious in cases of familial retinoblastoma multiple polyposis of the large intesting or verodermy pig mentosum and rarely a family such as that described first by Wirthin and Itter by Hauser and Weller shows so many members in successive generations with some other particular land of cancer that an inherited predisposition eannot be doubted. Most supposed "enner families, however exemplify only the laws of chance."

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Blank (1944) has given a useful recent review of the genetic aspects of cancer and has particularly stressed the point with which the present chapter opened namely, that cancer is not a unit disease. Tumours of different sites and types differ in their genetic behaviour. And again we must inquire separately for each tissue and type of the disease whether any hereditary factors direct or indirect are involved in a specific form of the malady

The available statistical and experimental evidence shows clearly. I think that while an inherited predisposition to particular kinds of tumours is sometimes discernible and is in occasional special instances paramount by far the larger number of human cancers is due to carcinogenic chemical or other stimuli which are probably effective in most adequately exposed individuals whatever their genetic inheritance

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in their proneness to tumours in general, and to tumours of specific kinds. Con sidering only animals of comparable ages, guinea pigs and rahhits develop tumours much less frequently than rats or mice. Pigs and sheep less frequently than other domesticated animals, and cats less frequently than dogs.

TUMOURS IN MAMMALS

(1) Primates

Tumours of primates are of course of special interest for comparison with their human counterparts, but very few examples have heen reported In Ratchife's large series of animals (1933), primates had the lowest incidence of tumours of all mammals. This was clearly due in great part to the ages of the animals, for the average exhibition period of all the captive primates was very low as compared with other mammals, and the few tumour hearing monkeys were all elderly. The malignant tumours included two adenocarcinomas of the pancreas, an epidermoid carcinoma of the cardia of the oesophagus, and a fibrosarcoma of the ulna, all in Old World monkeys. In 1940 Ratcliffe also reported renal adenocarcinomas in four members of one family of thesus monkeys. Engle and Stout saw carcinoma of the prostate in an old macaque, and Steiner et al two instances of carcinoma of the tongue in monkeys.

(2) Dogs

Tumours are very common in middle-aged or old dogs, and in structure and behaviour many of them closely resemble, while some differ in instructive ways from their human counterparts. The following tabular summary of 204 canne tumours collected by Dr. H. B. Rudduck of Melbourne and studied microscopic ally by me, indicates the relative frequency of the growths encountered (Some of these were reported in 1938)

The figures of Sticker, Murray, Feldman, Antoine et al and others also, show the most frequent canine tumours to include fibro adenomas and carcinomas of the breast, papillomas and carcinomas of the skin, carcinomas of the oral cavity and pharynx, melanomas, testicular tumours, leiomyomas and lympho sarcomas Carcinomas of the gastro intestinal tract are extremely rare, and those of the other internal viscera not common, the least uncommon sites being thyroid, ovaries hladder and prostate. The infrequency of alimentary and other visceral tumours in dogs is certainly not wholly attributable to their remaining Rudduck's and my specimens were from a nearly consecutive series of surgical and necropsy cases, in which deliberate search was made for tumours of all kinds, yet only one example of gastro intestinal tumour, a carcinoma of the cardia, was found As in Antoine's series, no special proneness of any particular hreed of dog to any particular tumour was noticed Tumours which were frequently multiple in the affected animals included mammary fibro adenomas (5 cases), sebaceous adenomas (2 cases) adrenal cortical adenomas (bilateral in both cases) carcinoma of the hreasts (5 cases) carcinoma of the liver (2 cases) papillary carcinomas of the ovaries (bilateral in both cases), melanomas (7 cases), and tumours of the testes (10 cases)

CHAPTER 6

TUMOURS IN ANIMALS

THE OCCURRENCE of particular kinds of tumours in animals will be referred to in the respective chapters of Part II. Here a brief outline of the main tumours occurring spontaneously in different classes of animals is given and their trans plantation and other experimental methods of studying their properties are discussed. Much of value for human pathology is yet to be learnt from the study of animal neoplasms. More use should be made of the pathological material passing through the hands of veterinarians breeders and slaughtermen most of which is wasted. Sticker (1902) was one of the first to attempt a comprehensive survey of cancer in domestic animals but his outline contains little pathological detail. Murray's papers (1908) are an important early contribution to the scientific study of animal tumours and the monographs of Fox (1923) and of Feldman (1932) and the papers of Cramer (1932) and Ratchiffe (1933) are the best general accounts.

THE AGE DISTRIBUTION OF ANIMAL TUMOURS

In assessing the relative frequency of any particular kind of tumour or of tumours in general in different species of animals the ages of the animals examined are of prime importance. Most spontaneous tumours in animals as in man occur in middle aged or elderly animals. Thus in Sticker's series more than two thirds of the horses with carcinoma were over 10 years old and about two thirds of the dogs with carcinomas were over 6 years old. Of 204 dogs with tumours (of all kinds) examined by Rudduck and myself the ages of 170 were known of these 147 (86 per cent) were over 6 years of age. Of 39 sheep with tumours, examined by Feldman 21 were designated old or aged. Mice with spontaneous tumours are usually at least eighteen months or two years old. and rats with tumours are usually between 2 or 3 years old. The increasing incidence of tumours with increasing age. In all genera of both mammals and birds is strikingly shown in Ratcliffe's records.

Clearly then tumours will be found much less frequently in animals which are often slaughtered for food at relatively early ages such as sheep cuttle and pigs than in domestic pets such as dogs and cast which often survive into old age. In mice rats guiner pigs and other hiboratory animals which are often under close observation for long periods such tumours as occur will be found relatively frequently. It is impossible to estimate the frequencies of tumours in wild animals because their ages are unknown—but that all species are prohably susceptible to tumours is shown by the observations of Fox Ratcliffe and others on neoplasms in captive animals.

However when due allowance has been made for the relative differences of the proportions of the normal life spans attained by the several species of domestic and laboratory animals it is clear that these species do differ intrinsically

(3) Cats

96

Tumours are decidedly less frequent in eats than in dogs. The commonest sites are the breast and skin. Rudduck and I studied 8 tumours from eats. 2 adenocarcinomas of the panerers, and one case each of adenocarcinoma of the liver, basal cell carcinoma of the skin, fibrosarcoma of skin, neurogenic sarcoma of skin, chondrosarcoma of the humerus, and angiomatosis of the liver

(4) Horses

Tumours are more common in horses than in other ungulates of corresponding ages The commonest sites of carcinomas are the skin, penis, vulva, nasal cavity and sinuses, conjunctiva, oral cavity and kidney Tumours of the breast are relatively infrequent Adenomas of the thyroid, leiomyomas of the alimentary canal and lipomas are not uncommon Cutineous melanomas are frequent, especially of the tail or perineal regions of old grey animals Squamous cell carcinoma of the cardia is well known Teratomas of the testis, not infrequently multiple and bilateral, are more frequent in the horse than in any other species Lymphoid tumours appear to be less common than in other mammals Rudduck and I studied the following tumours from 25 horses papil lary squamous cell carcinoma of the conjunctiva 13 cases, teratomas of the testes 5 cases, and one case each of squamous carcinoma of the penis, squamous carcinoma of the vulva carcinoma of the breast carcinoma of the ovary, adeno carcinoma of the thyroid, neurofibroma of the skin, and fibrosarcoma of the skin

(5) Bovines

The commonest tumours of cattle are squamous carcinomas of the conjunctiva, carcinomas of the skin of the udder, lymphosarcomas and uterine myomas Carcinoma of the uterus, ovary, liver, rumen, or thyroid are less common, carcinomas of the true stomach, intestines or mammary gland are rare Tumours of the adrenal cortex are well known Rudduck and I examined 5 tumours 3 squamous carcinomas of the conjunctiva, a squamous carcinoma of the perineum, and an adenoma of the adrenal cortex

(6) Sheep

the two most frequent sites are the Epithelial tumours are relatively rare adrenal glands and the liver (Feldman)

Lymphoid tumours and uterine leiomy

omas occur

Rudduck and I saw the following three tumours in sheep—a chondrosarcoma, a lymphosarcoma and a papilloma of the gall bladder

(7) Pigs

Epithelial tumours are rare Melanomas, leiomyomas of the uterus and lymphosarcomas are not uncommon. The commonest tumour of swine is embry once nephroblastoma usually in young animals and sometimes multiple and bilateral This tumour appears to be more frequent in the pig than in any other mammal

TABLE

| TY | PES O | r T | UMO | URS | | | | | No of dogs | Total |
|---|--------------------|-----------------|-----------------|--------------------|-----|----------------|----------------|------------|---------------|-------|
| Benign epithelial tumours | | | | | | | | | | |
| Fibro adenoma of brea | ast ~ | - | - | - | - | - | - | | 17 | |
| Papillary cystadenoma | of brea | st | - | - | - | - | - | - | 2 | |
| Papilloma of skin - | - | - | - | ~ | - | - | ~ | - | 4 | |
| Sebaceous adenoma of | skin | - | - | - | ~ | - | - | ~ | 4 | |
| Cystic hydradenoma o | f skin | - | _ | ~ | - | - | - | ~ | 1 | |
| Ceruminous adenoma | - | - | - | - | ~ | - | * | - | 3 | |
| Adenoma of adrenal c | ortex | ~ | - | - | - | ~ | - | - | 2 | |
| Adenoma of thyroid ~ | _ | • | ~ | - | ~ | - | ~ | - | 1 | 32 |
| (6 cases of adenor spaniels are omitt hyperplasias) | nas of ed as t | the | insd e are p | elid al robably | on! | m you m you | ni, co immi | tory | | |
| Carcinomata | | | | | | | | | | |
| Skin | - | - | - | ~ | ~ | - | * | - | 23 | |
| Breast | | - | - | - | - | | - | ~ | 15 | |
| Tonsil | ~ | - | - | - | - | - | - | ~ | 10 | |
| Alreolus of the jaw - | - | - | - | - | - | ~ | ~ | - | 2 | |
| Liver | ~ | - | - | - | ~ | - | | - | 6 | |
| Ovaries (papillary 2 g | ranulosa | 1) | - | | - | ~ | - | - | 3 | |
| Other (thyroid cardi- | 3 0300 | reas | lung | eyelid | pro | state | salts | ary 1 | | |
| bladder) | | - | - | - | - | - | - | - | 8 | 67 |
| Tumours of testis | | | | | | | | | | |
| Interstitial-cell tumour | | _ | - | _ | _ | _ | _ | - . | 16 | |
| Seminoma | | _ | _ | _ | ~ | - | - | - | 7 | |
| Rete or Sertoli cell tur | nave. | _ | - | _ | _ | - | - | -1 | 4 | 27 |
| | | | | | | | | Í | | |
| Melanoma (malignant 11 | benign (| 6 da | rubtful | 5)- | - | - | - | ~ | - | 22 |
| Benign non epithelial tumo | urc | | | | | | | - 1 | | |
| Lesomyoma | _ | - | - | - | - | - | - | - | 6 | |
| Fibroma | ~ | - | - | ~ | - | - | - | - 1 | 2 | |
| Lipoma | | - | - | - | - | | - | - ; | 2 2 2 | |
| Angioma | - | - | - | - | - | ~ | - | - | 2 | |
| Basophil-cell tumour (| see Char | nter | 51) - | - | ~ | - | - | ~] | 2 | |
| Chondroma | _ | - | - | - | - | ~ | ~ | ~ { | 1 | 15 |
| (16 cases of single are omitted because | or mul se doubt | t iple fully | lympi neopi | noid greater) | wth | s art E | he spi | loen | | |
| Malignant non epithelial to | mours | | | | | | | t | | |
| Lymphosarcoma - | _ | - | - | | | - | - | - ' | 16 | |
| Osteogenie sarcoma - | - | ~ | - | | | ~ | ~ | - ; | 6 | |
| Fibrosarcoma | - | ~ | - | - | ~ | - | ~ | - { | 6 | |
| Angiosarcoma | - | | - | - | - | - | - | - [| 2 2 | |
| Leukaemia | - | - | - | - | ~ | - | - | - [| 2 | |
| Chondrosarcoma ~ | | - | ~ | - | - | - | - | -1 | 1 | |
| Other sarcomas - | <u>~</u> | - | - | - | - | - | - | - | 7 | 40 |
| Carcin s-sarcoma of therei | 1 - | - | - | - | - | - | - | - 1 | 1 | 3 |
| - | | | | | | | | | | |
| | | | | Total | AL. | - | _ | - | | 204 |

Squamous carcinoma of the skin is uncommon Rudduck and I examined a subcutaneous lipoma from a parrot, a subcutaneous myxoma from a parakeet, and a papillom of the claw base from a magpie The filterable sarcomas of fowls form a distinct and peculiar class (Chapter 4) Most avian tumours are not transmissible by filtrates

TUMOURS IN THE LOWER VERTEBRATES

Records of neoplasms of the cold blooded vertebrates are relatively scanty Reports of piscine tumours are more frequent than those of reptilian or amphibian—probably because of the wholesale capture and examination of fish as food Sufficient records exist to show that fish are subject to a great variety of neoplasms, and to show that, were reptiles and amphibrans of the same economic importance as fish tumours would probably be found as frequently in them also

(1) Γ₁sh

In 1904 Bashford and Murray referred to 7 examples of tumours in fish, in 1929 Takahashi collected 142 examples, and in 1933 Haddow and Blake reviewed reports of 174 piscine tumours and added 6 personally studied examples. Of the total 180 specimens, 114 were benign osteomatous or chondromatous tumours and 2 others were osteosarcomas. Other tumours included fibroma lipoma angioma rhabdomyoma, soft tissue sarcomas, carcinomas of the mouth and gill region melanomas, and ganglioneuromas. Visceral carcinomas were rare Many different species of fish were affected—teleosts, as might be expected, easily preponderating.

In addition Gordon and Smith (1938) have made detailed studies of peculiar melanotic growths in hybrid fish, and Lucke (1942) has given an admirable account of subcutaneous neurinomas in 76 fish from 3 species of the snapper family

(2) Amphibians

In his studies of adenocircinomas of the kidneys of leopard frogs. Lucke (1934) gave also a valuable review of previously reported tumours in amphibians. These included—in frogs, adenomas and adenocarcinomas of the skin glands adenocarcinomas of the kidneys, sareomas of the extremities, a car noma of the overy, and a fibroma of the mouth in salamanders two fibrorias of the feet, and a carcinoma of the testis and, in a trition, a carcinoma of the skin glands. Several of these tumours were reported, along with excellent figures by Murray (1908). Lucke (1937) has reported a myxosarcoma of the dorsal fin of a tadpole. Briggs successfully transplanted Lucke's renal adenocarcinoma of frogs to various sites in tadpoles. A carcinoma of a frog's liver is depicted in Fig. 196, Chapter 24.

(3) Reptiles

Lucke (1934) reviewed records of 11 reptilian tumours namely a fibroma in a python, carcinoma of the ovary in a python three cases of multiple papillo mas of the skin in lizards, multiple enchondromas in a monitor, carcinoma of

(8) Rabbits

Spontaneous tumours in rabbits are infrequent. By far the commonest are adenomas and adenocarcinomas of the uterus (Polson Fardeau Burrows) Next in frequency are embryonic renal tumours and lymphosarcomas and other sarcomas. All other kinds of tumours are tare

(9) Guinea pigs

Tumours are extremely rare less than a score have been reported (Twort and Twort, Maury) These have included caremomas of the breast, sarcomas and ovarian and adrenal (umours

(10) Rats

Tumours of many kinds occur frequently in rats (Bullock and Curtis Curtis et al. Ratcliffe 1940. Wright et al.) The commonest of these include beingn fibro adenomas of the breast fibromas and fibrosarcomas of the skin lympho sarcomas carcinomas of the uterus and beingn thymic tumours. Carcinomas of the skin and breast are much less frequent than in mice. Embryone renal tumours usually in young animals are relatively frequent. Osteogenic sarcomas are well known. Surcomas of the liver associated with parisitie cysts constitute a special class (see Chapter 4). Curtis et al. found that different breeds of rats showed different incidences of particular tumours. One breed had many thymic tumours another breed many mesenteric sarcomas, and another breed many mesenteric sarcomas and another breed many mammary, uterine and skin tumours. The mammary fibro adenomas of rats are transplantable, and this has proved of great value in elucidating the composite neo plastic character of these growths (see below).

(11) Mice

It is necessary only to mention the well known mammary cutaneous pulmonary and lymphoid tumours of mice and to refer to Murray schosical page on mouse tumours and to the many papers of Sly. Holmes and Wells for further information. As in other domestic animals alimentary carcinomas are rare Different pure strains of mice differ very greatly in the spontaneous mendence of particular tumours so that in carrying out any experiments on carcinogenesis it is of prime importance to ascertain the natural tumour incidence of untreated mice of the breed used. Many fallacious or doubtful interpretations of experimental results have been made through neglect of this obvious requirement

TUMOURS IN BIRDS

The commonest spontaneous tumours of fowls and probably of many other birds also are lymphosizeomas and lenhaemas (well summarized by Feldman Chapter 14) careinomas of the ovary or oxiduct (Joest and Ernesti. Eber and Kriegbrum) and adenocareinomas of the intestine. Embryonic renal tumours fetomyomas of the alimentary canal or oxiduct, and various types of sarcomas are also well known. Ratchiffe (1933) found that renal adenomas or adenocareinomas were frequent in one species of parakeet. There have been several reports of gliomas of the bruin in fowls and other birds (Belmonte Jungherr and Wolf)

considerations are therefore irrelevant. Confirmation of this important principle has been the major result of the study of transplanted tumours

Since tumour transplants often act as antigens in unrelated animals of one species, it is not surprising that heterologous transplantation between different species is rarely successful. Many early attempts were made to transfer human tumours to animals, but with no genuine successes. That such transference is not necessarily impossible under special conditions, however, is suggested by Greene's findings (1942), that human sarcomas and carcinomas may survive successive passages in the aqueous cavities of the eyes of guinea pigs and rabbits. More successful hetero-transplantation has occasionally been achieved between animals of closely related species. Fujinami's myxosarcoma of the fowl is transferable to ducks, and an Ehrlich mouse carcinoma can be transplanted to rats.

The immunity reactions to foreign cells or proteins evoked by tumour trans plants limit the value of these in research. If transplantable tumours are used in a research as for example to study the effect of a particular treatment on a large number of animals all carrying similar tumours then non specific immunity reactions must be minimized by using a closely inbred homogeneous strain of animals and a tumour which has arisen in that strain. Otherwise, irregularities of natural and acquired resistance, corresponding to genetic and antigenic differences in the test animals will vitiate the results The complexity of the serological problems created by the use of transplantable tumours in a non homogeneous strain of animals is well presented in a paper by Gorer (1938) For these reasons transplantable tumours are now much less in favour than formerly and experimentalists prefer whenever possible, to use spontaneous tumours or tumours evoked by chemical or other carcinogens Certain special experiments in which tumour transplantation has proved of value in elucidating particular problems may now be outlined

(2) The study of metastasis using transplanted tumours

While many of the problems of metastasis can be studied as well with spon taneous or induced tumours as with transplanted ones, for some purposes the latter are preferable. Thus, by intravenous injections of finely divided transplantable tumours, disseminated growths may be obtained in the lungs, and several workers have used this method to study the fate of tumour emboli following their arrest in the pulmonary vessels (references by Willis, 1934) Similar experiments using ascitic fluid containing tumour cells, were performed by Wibeau and by Warren and Gates and Eisen obtained pulmonary growths by intravenous injections of emulsions of a mammary adenocarcinoma in rats

Several workers (cited by Willis, 1934) have used large batches of animals bearing transplanted turnours to investigate whether or not injury or manipulation or massage does aggravate dissemination, careful excision or incision of the turnours has little or no effect. For reasons already given, however, it is preferable that spontaneous or induced turnours should be used in such experiments.

The claims of Blumenthal Gross and others, that tumours could be evoked in mice and rats by injections of blood, exudates and cell free material from the foot in a tegu, adenoma of the thyroid in a turtle, adenocarcinoma of the stomach in a turtle sarcoma of the heart in a turtle and Scott sease of sarcoma of the liver in a crocodile with metastases in the heart and cerebellum Ratchiffe (1935) saw adenocarcinoma of the pancreas in a snake

TUMOURS IN INVERTERRATES

Very few instances are recorded. White dissected a large number of honey bees and found only one tumour, a lobulated fibroma of the thorax possibly of nerve sheath origin. Smith described a large pedunculated mesenchymal tumour attached to the pericardium of an oyster and found two other reports of tumours in molluses—one closely similar to his own and the other a pedunculated adeno fibroma of the pallium of a mussel

THE EXPERIMENTAL TRANSPLANTATION OF TUMOURS

Towards the close of last century it was discovered that some of the tumours of animals could be transferred by grafts to animals of the same species, and that some of these transplantable tumours could be propagated from animal to animal for an unlimited number of transfers. Such easily propagable tumours were eagerly sought after many of them were named after their discoverers, e.g. Jensen mouse carcinoma, Jensen rat sarcoma. Flexner Jobing rat eareinomy, Brown Pearce rabbit tumour, and study of the behaviour of transplantable tumours engrossed a large part of the energies of cancer research. For details of this work, consult the Reports of the Imperial Cancer Research Fund. Nos. 2 to 5 (1905-1912) especially the monographic account by Bashford et al. (1908), and the excellent review by Woglom (1929)

(I) The limited value of transplantation experiments

It is now clear that the value of transplanted tumours in cancer research is finited. The hope formerly strongly held by many workers that these tumours would lead to important discoveries in the subject of tumour immunity is now seen to have been a vain one. The very phenomena which aroused this hope are those which place struct limits on the value of researches with transplantable growths. A brief summary of the relevant facts is necessary

Early workers with transplantable tumours soon noticed irregularities in the success of grafts some grafts took while others under identical conditions failed. These differences were ascribed correctly to differences in host resistance. It was found that animals in which grafts had failed or had retrogressed after an initial take were resistant to further grafts—the hope was raised that clucidation of the nature of this resistance might lend to practical methods of tumour prophy laxis and therapy—Then—however—it was found that resistance to tumour transplants could the produced equally well by inoculations of normal homologous ussues—especially embryonic skin—The resistance so conferred had no effect on an existing spontaneous tumour or on the hibbity to develop one—This resistance whether natural or induced—was indeed only a general resistance equants foreign—tissue grafts—not against neoplastic cells in particular—Spontaneous tumours consisting of a creature's own tissues—cannot act as antig its and serological

brought about by the epithelial parenchyma." Foulds noted "the close resemblance between the fowl carcinoma and mixed tumours of the human salivary glands", and rightly concluded that "in this type of mixed tumour, only the epithelial component is neoplastic."

In this connexion, the common mammary fibro adenomas of dogs are of neculiar interest. In these tumours bone and cartilage are common, e.g. in 7 of the 17 dogs in Rudduck's and my series, and in many of those reported by Schlotthauer (1940) While spuriously cartilaginous appearances are often pro duced in these tumours by inclusion of isolated epithelial cells within secretory products or hyaline stroma, true cartilage and bone, the result of metaplasia in the connective tissue of the tumours, also occur frequently But, as we have already seen, this connective tissue is not a simple stroma but a truly neoplastic component Hence, bone and cartilage derived from it must also be of a mixed tumour neoplastic. The occasional osteogenic sarcoma of the breast, such as Schlotthauer's case 7, doubtless always arises from neoplastic bony tissue developed by metaplasia in the fibromatous component of a fibro adenoma. It would therefore be of special interest to ascertain whether any of the canine fibro adenomas could be transplanted, and, if so, to study the behaviour of their components in successive passages

Mention must be made here also of a subject which is more fully discussed in Chapter 8, namely, the apparently sarcomatous change which has been described as occurring in the stroma of senally transplanted turnours Haaland's classical account (1908) gives the fullest description of the changes observed, with many excellent microphotos but, in my opinion even these fail to exclude the possibility—indeed they even suggest the probability—that the supposed sarcomatous

tissue may have been anaplastic diffuse carcinoma

EXPERIMENTAL INVESTIGATIONS OF FACTORS INFLUENCING TUMOUR GROWTH

Spontaneous, induced or transplanted tumours in animals afford suitable material for controlled studies of factors influencing tumour growth and for controlled tests of agents of alleged therapeutic value. Alas a great proportion of the published studies of this kind are valueless, because of inadequacy of controls, insufficient appreciation of the wide limits of spontaneous variation in the behaviour of untreated tumours, variations related to age, nutrition general health of the animals and doubtless many other obscure factors and the use of unsuitable tumours e.g. tumours with a high degree of natural variation of growth rate or a high proportion of spontaneous retrogressions. Reliable research in this field cannot be carried out by novices but in the hands of the experienced using pure strain animals bearing tumours the behaviour of which is thoroughly known, valuable results are obtainable. A further important principle is that results obtained with one kind of tumour must not be assumed to apply to other tumours without direct verification.

Voegtlin (1937) has given a useful summary of the enormous amount of work directed to discovering the effects on tumour growth of various nutritional, bormonal and metabolic factors Conflicting claims have been advanced as to the influence of general nutrition particular proteins, amino acids, carbohydrates,

animals bearing transplantable tumours, have been shown by other workers (e.g. Flaks, Wagner) to depend on the transfer of disseminated tumour cells. Under suitable conditions then transplantation of tissue might afford a useful biological test for the presence of disseminated microscopic tumour deposits. Furth and Kahn found that a single leukacmic cell, isolated by means of a micro inpute sufficed for the transmission of mouse leukacmia. They showed also that cell free material from leukacmic mice or crushed leukacmic cells would not transmit the discuse, so that unlike fowl leucosis mouse leukacmia can be transferred only by means of intact malignant cells. Kahn and Furth found also that a beappyrene mouse sarcoma could be transmitted with 50 cells.

Transplantable tumours show individual peculiarities of metastasis and can be used to elucidate experimentally some of the factors influencing the frequency and distribution of metastases. One of the most interesting experiments of this kind was that of Foulds on the Brown Pearce ribbit tumour. Metastases from transplants of this tumour occurred frequently in the adrenals kindneys and eyes and less frequently in the liver and lungs—and a similar distribution of disseminated growths developed following intravenous inoculation. But in inimals vitally stained by repeated injections of trypan blue remarkable departures from the usual distribution of metastases were observed the spleen liver and lungs—were now the commonest metastatic sites. Evidently vital stuning had diminished the normal relative infertility of these organs as soils for metastasis. This experiment suge, sets a promising field of fluture research.

(3) The study of composite tumours by transplantation

If a composite or mixed tumour can be transplanted this affords a possible means of segregating or selecting its components and studying their behaviour separately. This has proved possible with the mammary fibro adenomas of rats (Robinson and Grauer Heiman and Emge). Heiman and Emge found that the fibromatous component can be obtained in pure form by repeated transfer and that this component may eventually undergo sarcomatous change. The resemb lance of these characters to those of human mammary fibro adenomas is obvious and the experimental results afford evidence that the connective tissue component of these growths has genuine neoplastic properties and is not merely a stroma to the entitletium.

It would be of great interest to early out similar studies with teratomas and embryonic mixed tumours of the kidney occurring in animals and to ascertain whether their components could be segregated by transplantation. The goundal teratomas of fowls and horses and the nephroblastomas of fowls rabbits, rats and pigs afford possible material for such research. Transplantation of careino sarcomas of the dog's thyroid such as that described by Rudduck and me might enable separation of the epithelial and sarcomatous elements.

Occasionally a transplanted tumour induces in the host stroma metaplastic changes study of which throws light on some of the supposedly instead tumours. Thus Foulds studied a transplantable carcinoma of a hen so viduet in transplants of which bone and cartilage were prominent giving the tumours a mixed structure. These selected tissues however were formed by the losts connective tissue cells which were constrained to differentiate in this way he conditions.

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fats, lipoids, the several vitamins, various acids and bases and inorganic salts but no conclusive or generally significant results have eventuated. Claims have also been made for the efficacy of extracts of spleen placenta embryonic and other tissues, or of feeding with these tissues but again the results are conflicting and undependable. While we know that the growth of some mammary and prostatic carcinomas is influenced by oestrogenic and related hormones there is no experimental evidence to show that insulin thyroxine parathormone. adrenaline, cortin or the pituitary hormones have any consistent influences on tumour growth in general

Many of the claims for the therapeutic value of particular diets hormones vitamins tissue extracts bacterial products and other substances in the treatment of tumours have been urged with such lack of evidence and such unreasoning vebemence as to show the claimants to be either deliberately fraudulent or the victims of obsessions-and it is often difficult to distinguish between fraud and obsession Subjection of any therapeutic claim to an adequate biological test on a large number of turnour bearing animals under properly controlled conditions is a big undertaking, and not to be lightly embarked on unless the claim has a substantial basis

Experimentalists and clinicians alike have harboured the hope of discovering some chemical agent which might selectively inhibit tumour growth or damage tumour cells. Lead selenium colchieine isamine blue and other dyes have been amongst the substances which have raised false hopes of success. Clearly any substance presumed to possess cancer inhibitory properties should be tested on a large scale on tumour bearing animals before being applied to human sufferers In the past much harm has been done by the indiscriminate and premature administration to human beings of supposed remedies which could and should have been tested first on animals. The excuse has usually been that the victims of hopeless cancers should not be denied the possible curative or palliative effects of new remedies pending their testing on animals-in excuse that has been responsible for a great deal of avoidable physical and mental suffering to say nothing of a great deal of exploitation by quacks and cranks

The most interesting researches on factors affecting tumour growth are those of Haddow and his co workers on the inhibition of growth effected by the adminis tration of carcinogenic agents. These are discussed in Chapter 8

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CHAPTER 7

THE MODE OF ORIGIN OF TUMOURS

INTRODUCTION

THE MODE of origin of tumours, while clearly a matter of fundamental biological interest as well as of practical importance, has been strangely neglected or mis understood by many modern pathologists. The most prevalent view has been that each tumour has a simple unicentric origin, arising at a single point in time, from a single small focus of cells, and enlarging only by multiplication of these cells and their descendants. This strict unicentric view is largely a legacy from Cohnheim's hypothesis of embryonic rests, which precluded the possibility of progressive cancerous change in neighbouring adult tissues. Although Cohnheim's hypothesis of the origin of tumours from superfluous embryonic cells has been abandoned by most modern pathologists, his concept of restricted unicentric origin and purely intrinsic growth has largely persisted. The prevalence of this view may be gauged from the following citations from well known works on tumour pathology.

Mallory (1923) insisted that 'Tumors grow entirely by multiplication of their own cells, not by transformation of normal cells into tumor cells', and that attempts to trace gradations between normal and neoplastic tissues are "founded on incorrect observation, interpretation and deduction" to McFarland (1924) 'It seems well to think of a tumor as beginning at a minute focus starting, as it were, from a single cell or group of cells, and increasing in size through multiplication of the particular elements concerned There seems to be no ground for assuming continuous transformation of normal tissue into tumor-no successive beginnings' Kettle (1925) said, "It is generally held that tumours arise from one cell or group of cells, and not as the result of a change affecting a comparatively large area Whatever may be the size of the tumour, all its cells are the direct descendants of the mother cells or cells after briefly discussing the possibility that tumours may develop by progressive neoplastic change in a field of tissue, concluded yet these instances of lateral extension of tumor processes, if they eventually stand the test of criticism, are rare, and it should be emphasized that the great majority of tumor cells are isolated in origin and throughout their history"

This chapter is to show that the strict unicentric view is false and that tumours arise from small or large fields of tissue and enlarge not only by cellular proliferation but also by progressive neoplastic conversion of tissue within those fields Careful microscopic study of early tumours of many kinds affords clear evidence of such progressive change, with plain transitions from normal to neoplastic tissue. In many cases the extent of the potentially neoplastic field is much greater than the small size of the initially appearing tumour would suggest a point of great surgical importance.

The modes of origin of tumours of the various classes will be discussed and

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of these zones is nearing exhaustion. The structure of the transition zones in these specimens, as also of others described in my papers cited is quite unlike the familiar picture of previously normal epidermis suffering invasive replacement by an advancing tumour and no ingenious explanations, such as MacCallum's secondary healing together will suffice to make the supposition of a simple unifocal origin plausible.

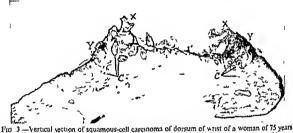


Fig 3 — Vertical section of squamous-cell carcinoma of dorsum of wrist of a woman of 75 years who had multiple keratoses of hands and face XX = crater left by detachment of horny mass XY = zone of transition from hyperplistic to neoplastic epithelium CC = deeply penetrating concerous downgrowths (x 4)



Fig. 4—Vertical section of squamous-cell carcinoma of neck of man aged 70 XX = crateriform in of growth EE = marginal epidermis like downgrowths of tumour CC = active poorly differentiated carcinoma sharply delimited from E at the arrows DD = thick layer of alterid dermal elastic tissue (X6)

As my previous papers showed, during the early stages of cancerous transformation of a field of prepared epidermis the structure observed may be further complicated by—(a) invasive invagination of the epidermis as it undergoes illustrated in Part II of this work. The following paragraphs necessarily partly traverse the same ground, but with stress on the general aspects of the subject

FIELDS OF ORIGIN OF EPITHELIAL TUMOURS

(1) The epidermis

The sequence of changes taking place in skin destined to give origin to tumours is best followed in experimental material which can be properly controlled and studied at all stages as in the experiments of Deelman Orr Brunschwig and Tschetter and Glucksmann However the pre-cancerous and early cancerous changes observed by experimentalists, described in Chapter 4 find their close counterparts in human pathology. The changes seen in pre-cancerous lesions of the skin such as keratoses X ray dermatitis, arsenical dermatitis and chronic ulcerative lesions and the transitions from these to carcinoma, parallel those seen in the genesis of experimental growths of the epidermis.

Elsewhere (1944 and 1945) I have depicted the structure of early squamous-cell eartenomas of the skin and lip, confirming the much earlier conclusions of Lohmer (1900) that these do not have a simple unifocal uni temporal origin and purely

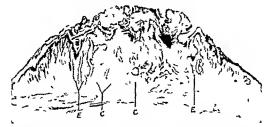


Fig. 2—Vertical section of squamous-cell careinoma of dorsum of hand of a tar worker aged 56 EE = downgrowths with perfect epidermal structure | CC = atypical downgrowths. (× 7½)

intrinsic proliferative growth. Figs. 2 and 3 depict examples of such tumours which show—(a) gradual hyperplastic thickening of the surrounding epidemia as it approaches the growth (b) gendle transition from the hyperplastic to the neoplastic epithelium making it impossible to decide just where the one ends and the other hegins, and (c) retention by the cancerous epithelium of the general architecture of the epiderims but with extravagant papillation keratinization and some downward invision of the derivas. The tumours display plain evidence of a progressive hyperplastic neoplastic change still taking place, in a centifugal direction over fields of epiderims greater in extent than the present sizes of the growths are at least 1.5 centimetres in diameter. Probably the actual size of the potentially cancerous field is much greater than this since there are wide zones of epiderimal hyperplastic around the growths and there is no reason to suppose that we have chanced to examine the tumours just when the neoplastic potentiality

not one cancerous focus, but of several simultaneous foci, in a field of abnormal epidermis, (c) the appearance in the deeper invading parts of the tumour of more anaplastic downgrowths, clearly indicative of augmented rate of growth and invasive characters (Fig 5), and (d) the invasive replacement of the less active neoplastic epidermis by the more anaplastic component (Fig 4)

Of course it is not denied that an established tumour grows in bulk by cell proliferation in excess of that of the normal epidermis. What is to be insisted on, however is that a skin caneer in its early formative stage arises more by a general transformation of pre existing epidermis than by cellular multiplication and that only after the formative field has all suffered neoplastic change does the tumour grow solely by multiplication. The two processes, neoplastic transformation and proliferation, overlap, the former predominating during the early genesis of the tumour, the latter often being initially negligible but gradually taking an increasing, and finally exclusive, part in the growth of the tumour

While solitary localized epidetmoid growths of the skin often have a field of origin demonstrably of at least 1 or 2 eentimetres in diameter, in the ease of multiple growths or of certain extensive superficial carcinomas the potentially neoplastic field is much greater than this. Thus in cases of multiple squamous-celled growths of the face and neck seen in fair-skinned people with widespread keratoses due to long exposure to light from outdoor occupations the whole of the epidermis of exposed areas is ready to become cancerous and the multiple tumours which actually develop merely denote the foci of maximal cancer potential in these areas. The extreme instance of this is seen in the rare disease xeroderma pigmentosum in which there is an inherited predisposition of the epidermis to neoplasta, and at an early age the patients develop numerous carcinomas of any areas of skin exposed to light. The inadequacy of the unicentric view in such cases is obvious, the cells of the entire epidermis in the susceptible areas are in an unstable pre cancerous state and many of them undergo cancerous trinsformation in situ

So also it is clear that many skin cancers arising in association with scars or chronic ulcers or sinuses are not of simple unifocal origin but exhibit progressive cancerous change over more or less extensive sometimes multiple, areas of the epithelium clothing the scar or surrounding the ulcer (Figs 6, 7 and 8, and Willis, 1945)

Bowen's so called "pre cancerous dermatosis" is ruther a form of widespread multifocal or diffuse cancerous transformation of epidermal cells m situ (Chapter 14) Paget's disease is probably of similar nature (Chapter 13) Vulval leucoplaka also, in some cases, is already a form of widespread intra epidermal carcinoma even before the appearance of the multiple areas of obvious growth which often supervene (Chapter 32) As long ago as 1897, Hauser carefully described a case of recurrent carcinoma of the vulva clearly arising progressively and in a wide spread manner in the diseased epidermis Squamous cell carcinoma arising in the skin of a cystic teratoma is sometimes demonstrably widespread in origin (Willis, 1937 and Case IV, Chapter 61)

The frequently multicentric or diffuse mode of origin of basal cell growths of the skin must be apparent to anyone who studies these tumours at all closely



Fig. 5. Vertical section of one half of a squamous-cell carcinoma of the pinna of a man of 57 years N= invagination fig at margin of growth. FE = surface rone of epidermis-like growth. CC = more action extremola. PP = catalage of car. (-16)

neoplastic change forming a characteristic invagination lip or circular rampart bounding an enlarging cancerous crater (Figs. 3 and 5) (b) the appearance of,

(Lohmer, 1900, Molesworth, 1927, Willis, 1945, and Figs 9, 10 and 11) Of the superficially spreading type of rodent carcinoma Molesworth said, "the main tumour mass is being reinforced continuously by exactly similar cells produced



Fig. 8—Extensive superficial epidermoid carcinoma of a deep sinus of the buttock in a woman of 28 years (Case I Chapter 14) (×8)

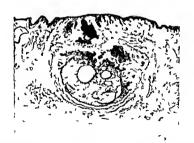
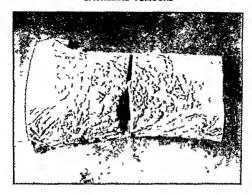
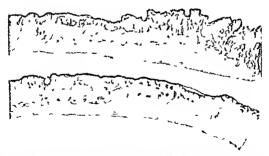


Fig. 9—Small basal-cell carcinoma of the cubital fossa of a woman of 55 years who had also had multiple similar growths on the face neck and back. The structure points to simultaneous origin of the tumour from the interpapillary processes of the epidermis and a group of sweat glands and their ducts. (x 12)

not by reproduction from its own cells, but from those of neighbouring epithelium"
Farly specimens of the flat plaque like superficial basal cell carcinomas often





Fit is 6 and 7—Cancerous varicose ulcer from a woman aged 64. Fig. 6 is a general view following amputation—the transverse cleft is the site of temoral of tissue for prehiminary sections. Serial horizontal sections of the entire growth at planes. I contimetre apart were prepared Parts of two of these in the marginal region of the growth—are shown in Fig. 7—(1-1).

a large part of the body, many independent microscopic foci of growth may be found in skin not affected by visible growths (Fig. 11)

That cutaneous melanomas arise by a progressive neoplastic change from considerable fields of epidermal cells is clear from Dawson's classical studies. Describing the early genesis of malignant change in pigmented moles, he said, "Similar changes occurred throughout the whole surface extent of the epithelium involved both in the rete processes and the intervening epithelium." Under the heading "Multicentric origin of the cutaneous melanomata". Dawson also said,

In the study of the advancing margins of many of the malignant melanomata, especially those which showed zones of pigmentation fading off into the normal skin numerous appearances were observed which pointed definitely to the presence of multiple and isolated points of origin of the early malignant change in the surface epithelium of rete epithelial processes. Not merely at the immediate advancing zone did the tumour growth appear to be increased by the early change taking place in the eells as it were m situ in their epithelial connexion but—in the large sections where the epithelium was followed serially over a large area adjoining the actual tumour—numerous isolated groups of intra epidermal cells could be found undergoing a malignant transformation. The truth of Dawson seconclusions is fully attested by his many beautifully depicted specimens and can be confirmed by any unbiased student of a few early growths of this kind

(2) Epithelial tumours of mucous membranes

Early careinomas of the lip or tongue frequently show gentle transition from hyperplastic to neoplastic epithelium similar to that seen in tumours of the epidermis. Further, a careinoma of the lip sometimes shows clear structural evidence that it has arisen partly from the epidermis and partly from the mucosal epithelium, the downgrowths of the epidermal and mucosal halves of the tumour differing in the same respects as their parent epithelia (Fig. 12). In early lingual



Fig. 12—Sagittal section of carcinoma of lip from a man of 41 years. The downgrowths of the half of the tumour continuous with epidermis (X) are more pointed and more corruined than those of the half continuous with mucosil epithelium (Y). Also a distinct stratum granulosum was plesent in the former but not in the latter (x. 10).

earcinoma there is often absence of demarcation between hyperplastic and cancerous epithelium, and the latter forms downgrowths from an intact surface layer over a considerable area of mucosa (Fig. 13). Even some recurrent

show unmistakably their multifocal origin from many or all of the interpapiliary epithelial processes in the affected area. Early specimens of the more bulky subepidermal basal cell growths often show evidence of their multifocal origin

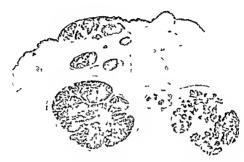


Fig. 10—Subepidermal basal-cell careinoma of leg of a woman of 43 years. Structure plainly shows simultaneous origin from at least two groups of sweat glands and their ducts. (× 8)

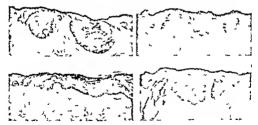


Fig. 11.—Panorame view of a piece of skin from a man about 55 years old who had numerous superficial basal-cell carcinomas on the face chest back and elbows. The sections show multicentric and diffuse origin from the epidemis. 1. 50.)

from several groups of sweat glands and duets or from several hair follieles and sheaths or from both (Figs. 9 and 10). At the margins of well-established growths it is not unusual to find small satellite foci separate from the main mass. In those not infrequent eases of very numerous basal-cell tumours occurring over

the disease, there is a gradual extension of the area of origin by the progressive transformation of normal into neoplastic alveoli. The extent to which the lateral growth proceeds by this method is difficult to determine. In some cases there is a very wide superficial tumor involving 10 to 15 cm of the mucosa, a form strongly suggesting a gradual inclusion of normal areas of mucosa." Tsunoda described a case of early gastric carcinoma with three separate areas showing transition from normal to cancerous epithelium. Konjetzny's opinion that gastric carcinoma usually arises in a multicentric or diffuse manner is convincingly supported by many excellent microphotographs (see also Chapter 21).



Fig. 14—Early recurrent carcinoma of tongue following radium treatment in an elderly woman showing an extensive field of similarly affected epithelium (× 10)

From my own studies, I am satisfied that the foregoing views are correct, and that gastric or intestinal carcinoma often arises, not from a single minute focus but progressively over a field of prepared mucous membranc of small or great area. In cases of multiple polyposis of the colon with supervening multiple carcinoma, the potentially cancerous field is the mucosa of the entire large intestine and m croscopic study will reveal many minute neoplastic foci unsus pected on naked eye examination.

Extensive diffuse carcinomas of hollow viscera, such as "leather bottle' carcinomas of the stomach and comparable growths of the biliary tract, are difficult to explain is the product of spread from a single original focus. Granting that these tumours are of a widely and diffusely infiltrating type, yet the walls of the viscus are often so uniformly affected over such extensive areas, sometimes the entire stomach or the entire extra hepatic biliary tract (Willis, 1942) that it is impossible to guess even approximately where the growth may have started first. It is much more plausible to assume that it arose, simultaneously or successively, over a large area or several areas of the mucous membrane. This supposition is supported by the occasional discovery of multiple separate areas of diffusely infiltrating carcinoma in these organs. Under the appropriate title carcinoma in situ., Mallory has described extensive superficial pre invasive gastric carcinomas although he speaks of 'replacement of normal by malignant cellis and does not affirm a widespread origin, the latter seems to me to be the obtained interpretation.

The linings of ovarian cysts display striking comparable examples of the simultaneous multicentric or diffuse origin of papillary growths from a predisposed epithelium. All pathologists are familiar with specimens of these tumours m which similar papillary growths have sprung from the linings of many separate loculi and often from those of bilateral tumours. Even in a unilocular cyst

carcinomas of the tongue show clear evidence of origin de noto from a more or less extensive field of epithelium (Fig. 14)

Although internal mucous membranes are less accessible for the study of the early genesis of timours, there is ample evidence that this follows stages analogous to those already described Early timours of the stomach intestine, urmary tract or uterus sometimes clearly show neoplastic transformation still in progress and especially in cases with numerous multiple growths, as in papillomatosis of the large intestine, all stages in the development of the neoplasms from the mucosal epithclium can be traced



Fig. 13 -- Vertical section of early carcinoma of torque from a man of 69 years. (x 71)

Long ago Hauser and Verse fully described early caremomas of the stomach and intestine which clearly showed origin from many or all of the glinds in considerable areas of the mucous membrane and marginal extension of the cancerous changes still in progress. Thus Hauser while fully recognizing difficulties of interpretation caused by secondary cancerous infiltration of the mucous membrane described and depicted appearances which alforded irrefutable proof that in the earliest stages of the development of cancer a primary cancerous change of the glands of the mucous membrane in their entirety without their disintegration can be observed. Of gristire carenoma kaufmann stid. It is certain that multicentric development is frequent sometimes indeed from almost all the glands in the entire stomach wall. According to Iwing during the formation of the original focus and to a variable extent thereafter normal frinds continue to be transformed into neoplatue structures. This lateral extension is more pronounced in the collo than in the stomach. Of intestinal carenoma Ewing concluded. In the cutly stages of most cases, and in some throughout

Benign mammary tumours, as well as malignant ones, often display clear indications of multicentric origin, and additive as well as proliferative growth In 1923 Cheatle first conclusively demonstrated that fibro-adenomas may be accompanied by satellite foci of growth and may enlarge by incorporation of these Nicholson confirmed this "The surrounding mammary lobules undergo the same minute changes that have already taken place within the body of the tumour, and are absorbed or incorporated into its substance" These conclusions can be verified by anyone who will take the trouble to examine microscopically the bed of mammary tissue in which a young growing fibro adenoma lies This usually contains multiple fibro adenomatous foci derived from hyperplastic mammary lobules and there is often plain evidence of the addition of these to the main mass. It is largely this appositional form of growth which gives many fibro adenomas a lobulated shape, they are lobulated because they are of progressive conglomerate origin Duct papillomas of the breast also are fre quently multiple sometimes very numerous, and occasionally quite diffuse Cheatle (1921, Fig. 208) depicted a breast with over 70 little intra duct papillomas, as well as three separate areas of carcinoma, and Cheatle and Cutler showed that papillomatous change may affect the whole extent of a single main duct and all its tributaries a condition which they aptly likened to multiple papilloma tosis of the colon

Multifocal neoplastic change of different types may be present in a breast As Cheatle and Cutler said, A breast which attracts clinical attention to one type of lesion is often a field in which other types of hyperplasia or neoplasia may be present and are likely to be present, the existence of which can be detected by the microscope." Full endorsement of this statement will be found in Chapter 13

(b) The prostate

There is no doubt that carcinoma of the prostate resembles that of the breast in frequently supervening on cystic hyperplasia and in frequently being multifocal or diffuse in origin. Early cancerous change, not infrequently discovered by routine microscopic examination of surgically removed enlarged prostates, is often clearly of multiple patchy distribution. I have examined a prostate which, though scarcely abnormal in either size or consistency, was found microscopically to hive undergone almost universal cancerous change in situ.

(c) The liver

Carcinoma especially liver cell carcinoma, arising in cirrhotic livers is frequently multiple the multiple growths sometimes being very numerous (see Chapter 24) Early tumours supervening on hacmochromatosis often have a distinct lobular pattern strongly suggesting that many separate liver lobules have undergone progressive cancerous change m situ (Willis, 1941)

(d) The pancreas

in 1936 I described an example of almost complete cancerous replacement of the pancreas without enlargement of the organ and with retention of normal lobular pattern, pointing clearly to the diffuse origin of the growth. Lohmer

papillomatous changes are often so extensive and so uniform as to preclude their origin from a single focus and indeed microscopically all transitions between quiescent cyst epithelium and papillomatous masses can be triedd pathological cysts of other organs also papillary growths may arise in a clearly multicentric or diffuse manner, as in my case of papillary carcinoma of congenital cysts in the liver (Willis, 1943)

(3) Glandular organs

(a) The breast

That mammary tumours often arise simultaneously or successively from extensive tracts of breast tissue is clear from the work of Cheatle (1921) Nicholson (1921) Cheatle and Cutler (1931) and Must (1941) To Cheatle belongs the credit of first demonstrating this conclusively in sections of whole breasts and for insisting that the primary cancer process transforming epithelial into malignant cells may commonly operate on extensive duct surfaces. Having been established at one part of a duct at may affect other parts of it or other ducts Nicholson endorsing Cheatle's conclusions said. I have insisted for years that hyperplasia passes insensibly into carcinoma and that this gradual change can nowhere be better studied than in the breast and that tumour formation is here multi centrie, or rather omni centrie. Muir expresses the same conclusions as Malignancy is often not only of multicentric origin but can be seen to occur gradually and to affect groups of cells in a diffuse fishion all stages of the process being traceable, the neoplastic change is regional rather than focal

I cannot understand how anyone who has examined cancerous breasts enrufully could fail to endorse these conclusions In Chapter 13 examples from my experience of multiple or diffuse origin of mammary carcinoma are described Sometimes multifocal origin is obvious enough even to the naked esc sectioning an amputated breast into serial slabs two or more clearly separate growths may be found instead of the expected one rarely even the clinici in is aware of the presence of two growths in the one breast or of simultinous primary growths in both breasts. More often multicentric origin is less obvious and is found only by microscopic study of various parts of the breast. Especially in cases of exercinoma supervening on cystic hyperplasm in addition to the main tumour there are often present in other parts of the organ inconspicuous papil lomatous or careinomatous foci only to be discovered by deliberate microscopic search. The ideal conduct of such search is by whole sections of the breast as described by Cherile but much may be learnt from multiple small sections from selected suspicious areas

Diffuse origin of executoma in part or the whole of a breast is not rare. Like Cheatle and Muir I have studied specimens of universally indurated shotty breasts, removed by the sure or because of persistent supposed, chronic mastitis and in which there was no clinical or maked eye evidence of localized tumef iction yet microscopic study has shown the entire breast to be cancerous and the disease clearly to have arisen not by spread from any particular initial focus but by simultaneous or rapidly successive neoplastic change of much or all of the mammary epithelium in situ. Cases of bilateral carcinoma of this type are not unknown and I have several specimens showing simultaneous diffuse carcinoms of all pairs of mammae in dogs

is also good evidence that simultaneous or successive multifocal neoplastic change occurs in these tissues (see Chapters 49 and 50)

FIELDS OF ORIGIN OF NEUROGLIAL TUMOURS

Most gliomas show absence of marginal demarcation from surrounding nervous tissue and many of them are quite diffuse. The surgeon often finds it impossible to determine even approximately the limits of the tumour, and its mingling with the normal tissues may be so gentle and so extensive that even microscopically its limits may be quite indefinite. In extreme eases the diffuse gliomatoses much or the whole of a ccrebral hemisphere or even a large part of both hemispheres may be diffusely affected, the tissues showing only slight general enlargement with blurring of normal markings but no localized tumour mass infiltrative powers of gliom's are admitted, there is little doubt that these highly offuse tumours are due to extensive origin rather than to extensive spread. Scherer all ccrebral astroeytomas should be con expresses this view as follows sidered as primary diffuse neoplastic proliferations of the neuroglia of considerable areas of the brain not as primarily circumscribed nodules with subsequent Study of my own material convinces me that this view is correct That astrocytic tumours are sometimes multiple and that separate growths of both diffuse and more localized types may coexist affords additional evidence of origin from fields of neuroglial tissue

MULTIPLE OR FIELD ORIGIN OF TUMOURS RELATED TO DEVELOPMENTAL DISTURBANCES

Many of those tumours which owe their origin to disturbances of early development show multiple and occasionally diffuse origin. This applies to neuroblastomas retinoblastomas nephroblastomas and teratomas. It applies also to neurofibromas angiomas and multiple exostoses and chondromas, though some of these are not true tumours. Multiplicity of any of the foregoing must clearly depend on influences affecting many parts of the developing tissues simultaneously. Sometimes the tumour-evoking effect of these influences may be universal throughout the entire field of similar tissue, e.g. the foetus described by Potter and Patrish showed generalized neuroblastomatous change in all of the sympathetic gangha, both adrenal glands and in some of the other viscera.

IMPLICATION OF FIELD ORIGIN REGARDING THE CAUSATION OF

Some of those who have correctly observed that tumours enlarge by spreading neglect transformation of surrounding tissue have supposed this to be due to some carcinogenic influence exerted by the tumour cells on their normal neighbours. Thus Welsh speaks of the passage of a malignant influence from cancer cells to adjacent non cancerous epithelial cells, whereby the latter are induced to become cancerous in situ. Molesworth speaking of the progressive genesis of basal cell carcinomas of the skin said. It almost appears as if the fever of proliferation were contagious. 'and again the 'tumour spreads by simulation of the neighbouring epithelium into activity identical with that which produced the original tumour mass by infecting it as it were with the fever which drove the original

long ago described panereatic careinoma in which—the tumour enlarged not only by intrinsic growth and replacement of surrounding tissue, but also by participation in the epithelal multiplication of fresh glandular tissue marginal to the tumour

(e) The salwary glands

Chapter 17 contains a description of the evidence which shows conclusively that the pleomorphic (so-called mixed) tumours of the salivary glands often take origin progressively from the surrounding glandular tissue. Direct trins formation of salivary acini into tumour can be seen and this change may be demonstrable at multiple widely separate places around or within the tumours.

(f) The testis

That seminomas may arise from extensive or multiple areas of seminal tubules is shown by the sometimes demonstrable multiplicity of these growths by their extensive replacement of testicular tissue without enlargement of the organ and by microscopic appearances pointing to progressive genesis features which are particularly well seen in early seminomas in dogs (see Chapter 33)

FIELDS OF ORIGIN OF NON EPITHELIAL MESODERMAL TUMOURS

The extent of the fields of origin of leiomyomas, lipomas meningiomas and many other non-epithelial growths is still uncertain. In many cases it is clearly small but its almost certainly not unicellulry and perhaps not even microscopic in size. Thus in the wall of the uterus the muscle fibres lie, not separately or chaotically but in compact groups and bundles and it seems likely that anatomical and functional units such as these would also be the pathological units and therefore the birthplaces of myomas. Careful study of serial sections of parts of the myometrium in uteri containing many small myomas supports this conception. The earliest recognizable myomatous foci are non-encapsulated whorled or fisciculated groups of fibres distinguishable only with care from normal tissue and even visible myomatous nodules may show at parts of their peripheries absence of clear demarcation between normal and myomatous tissue floweer there is little doubt that myomas enlarge chiefly by their own intrinsic problemation, and that additive growth is largely confined to unter young tumours.

Lipomas also may well arise not from single adipose cells but from lobules or groups of lobules of fatty tissue. Their subsequent growth may well be largely or entirely proliferative and intrinsic. However lipomas do occur which are not everywhere well demarcated from the surrounding tissue. and the possibility must be conceded that these may have enlarged by ancorporation of neighbouring lobules of adipose tissue.

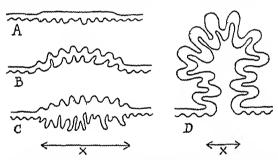
While many meningiorms by the time they are examined are large well circumscribed growths incapable of affording information as to their mode of origin the occasional extensive plaque like growths suggest an extensive origin from a considerable area of meningeal tissue

Neoplasms of the haemopotetic tissues the lenk-terms lymphosarcomatosis Hodgkin's disease and multiple myelomitosis have long been regarded by most pathologists as system diseases and although metastatic dissemination certainly plays an important part in the wide distribution of the lesions there

elevated part of the sessile growth is its centre, because here the tumour is oldest and excessive proliferation has been in progress longest, the bulk of the epithelium gets progressively less towards the periphery, because of the progressively less length of time during which neoplastic proliferation has been present

Should a papilioma have arisen m a relatively small field of epithelium and have thereafter grown considerably by proliferation, it will be of the pedunculated form shown in Fig. 15D with a narrow base corresponding approximately in extent with the initial area of origin and a prominently projecting mass of more or less complexly branched structure. The supervention of malignant change in such a tumour may at first bring about little change in its gross form, but later invasive growth is likely to enlarge the pedicle and occasion irregular ulceration.

Needless to say in many advanced malignant tumours of surfaces proliferative and invasive growth predominates and soon completely masks all evidence there may originally have been of marginal additive growth. Nevertheless, such evidence



1:10 15—The shape of a tumour as determined by its mode of origin A = epithelial tumour in situ B = sessile papilloma C = sessile papillomy carcinoma D = pendurculated papilloma of restricted field of origin X = eytent of origin

is not restricted to very early growths but may often be found if looked for in well-established tumours in which neoplastic change still in progress may continue to play a part in determining the form of tumour margins

In solid organs also the mode of genesis of tumours may determine their shapes. The most striking example, already mentioned is afforded by the mam mary fibro adenomas the lobulated form of which is clearly due in many cases to coalescence of multiple originally separate tumour lobules or to the addition of new tumour lobules at the margins of the main mass. Mammary carcinomas also "as show irregularly lobulated or branched outlines due to multifocal or diffure origin in a particular territory of tissue. The most notable instances of this are those, tumours which as described by Cheatle and Cutler, have arisen or are still arising from the entire extent of a main duct and all its peripheral branches

area of epithelium to proliferate. It has been suggested that this transferred contagion, might be a virus or perhips some special enreinogenic enzyme

However, in order to account for marginal additive growth there is no need to assume the existence of any mysterious enneer inducing influence or contagion passed from tumour cells to adjacent healths ones. As the foregoing account of diffuse and multifocal modes of origin shows, most kinds of tumours arise in more or less extensive fields of prepared tissue. The first spot to display visible neoplasia is only the region where neoplastic potential (compounded of intrinsic susceptibility of tissue and the incidence of all past extrinsic carcinogenic stimuli applied to it) was greatest. Extending outwards from this maximal point there is a field of diminishing potential covering a small or large area. and the tissue just marginal to the initial focus of neoplasia which is only slightly less prone to neoplastic change than the focal tissue itself soon follows it into active growth. Marginal addition is thus not an inductive effect of cancerous on normal cells, but merely the procressive response of the tissue field to which effective careinogenie stimuli have at some time in the past been applied a response the timing and distribution of which are determined by the intensity and distribu tion of those stimuli

In the light of experimental and occupational careinogenesis the sequences observed are indeed what might have been expected. Careinogenie agents are applied not to single cells or minute groups of cells but to many cells in considerable areas of tissue. All of the cells in the area are neted on similarly though of course not equally. The neoplastic change which is the end product of the response will usually take place not simultaneously throughout the tissue destined to undergo it but in a particular sequence dependent on the quantitative gradients of the effective original stimulation. That this concept accords with what is actually observed to take place in many tumours is strong evidence that they are due to external carcinogenic stimuli comparable with those used experimentally. Embryonic rests malignant influences or contagions in the tissues are superfluous assumptions.

THE INFLUENCE OF THE MODES OF ORIGIN ON THE GROSS FORMS OF TUMOURS

The extent of the field of origin and the relative importance of the two processes of neoplastic conversion and proliferation within that field are important factors in determining the shape of the resulting timour. Example, swill make this clear

Suppose neoplastic change to occur in many or all of the cells of a surface epithelium in situ with little proliferative increase in the number of cells. The tumnur will then appear only as an area of altered epithelium with little increase in bulk and therefore little elevation above the general surface livel. Bowen's intra-epidermal careinoma is such a tumour (Fig. 15x). and analogous tumours in mucous membranes are the early non invasive careinomas in situ of the alimentary tract described by Hauser Mallory and others.

Now suppose considerable proliferative increase in bulk in accompany early pringressive neoplastic change in a field of epithelium. If the tumour is non myasive that is a benign papilloma it will assume the form shown in Fig. 15n if invasive that in Fig. 15c. In Figs. 15n and 15c, the bulk-est and therefore most

tissue sometimes the whole breast, and since, as Cheatle and Cutler correctly a breast which attracts clinical attention to one type of lesion is often a field in which other types of hyperplasia or neoplasia may be present and are likely to be present, clearly mammary cancers or any other persistent lesions deemed arreversible and potentially cancerous necessitate complete removal of the affected organ. This is not to deny that strictly localized early cancers of the breast may sometimes be successfully eradicated by local excision as suggested by Fitzwilliams Nevertheless, local excision of mammary cancers in general even early ones is pathologically unsound, for there are many growths which, contrary to the prevalent assumption on which Fitzwilliams bases his conservative method do not start as a local change, perhaps one cell taking upon itself the characteristics and habits of malignancy's simple mastectomy will also be curative

For patients curable by local excision
For the much more numerous patients with tumours which seem to the chincian to be localized but in whom other parts of the breast contain undetected potential or actual cancerous changes simple mastectomy will sometimes be curative when local excision would certainly fail

HYPERPLASIAS AS PRE NEOPLASTIC STATES

Amongst the commonest sites of tumour formation are those tissues in which pathological forms of hyperplasia are frequently seen these include the breast uterus prostate thyroid and other ductless glands liver and skin Moreover, in all of these situations transitions from hyperplasia to neoplasia are frequent In the breast fibro adenomas are almost always situated in a bed of hyperplastic tissue and persistent cystic hyperplasia is an important pre cancerous state. In the uterus various kinds of abnormal endometrial hyperplasia are frequent and some of these pass insensibly into carcinoma. Carcinoma of the prostate frequently arises in an organ already the sent of benign enlargement. Most thyroid adenomas and carcinomas develop in glands already goitrous, and there is reason to believe that analogous hyperplastic strumas may precede the development of tumours of the pituitary gland adrenal cortex and other endocrine tissues. The close relationship of hepatic adenomas and careinomas to regenerative hyperplasia is well known. In the skin epidermal hyperplasias evoked by various irritative and inflammatory lesions sometimes become cancerous carcinoma may supervene in keratosis chronic ulcerative lesions around the sinuses of osteomyelitis, in X ray or radium burns and so on. In all of these cases it appears clear that the abnormal stimuli regenerative or hormonal, which call forth hyperplastic proliferation in the tissues-proliferation which is at first reversible should the stimuli cease to act-may should they persist eventually evoke progressive neoplasia as well. To the student of tumour causation, then, the nature and causes of hyperplasins are of fundamental interest

The obvious relationship of hyperplasta and neoplasta in certain cases however must not be allowed to mislead us. There are legion hyperplastas which never and internour formation and there are many tumours which develop without any recognizable previous hyperplasta. Clearly then the causation of a tumour involves more than the mere persistence of hyperplasta evoking stimuli. The specific nature of the stimulius is all important, for example on the experimental side both carbon tetrachloride and aminoazotoluene cause liver dynage followed

the tumour accordingly being of an irregularly pyramidal form with apex towards the nipple

THE SURGICAL IMPORTANCE OF FIELDS OF ORIGIN

As long ago as 1865 Karl Thiersch taught that recurrence of an enithelial tumour following surgical removal was not always due to incomplete removal of tumour tissue but was sometimes due to fresh cancerous change in the predisposed epithelium of the region. This view though based on good objective evidence was unfortunately superseded by the teachings of Cohnheim and Ribbert, whose unicentric views on tumour genesis though speculative and erroneous have strongly influenced pathological thought ever since. Hauser, Lohmer and others indeed strongly opposed Ribbert's sequestration hypothesis and advanced clear evidence for the progressive field origin of epidermal and other tumours and for the correctness of Thiersch's teaching regarding recurrence. However, in spite of the conclusive evidence presented by these workers many surgeons and pathologists even to day continue to assume that tumours take origin from single small foci of tissue, and therefore that recurrence following excision is due to incomplete removal of tumour tissue. Exposure of the falsity of this assumption has been the main theme of the present chapter. Thierseh was right, and Cohnheim and Ribbert were wrong, and the pathological basis of surgical practice must be clarified accordingly. The following instances will serve to show the great practical importance for the surgeon of correct views on the mode of origin of tumours

Because many solitary localized eareinomas of the skin and hip take origin from relatively small fields of tissue, they are successfully excised with no subsequent recurrence. But there are other cutaneous growths which, because of the extent of their fields of actual or potential origin carry much greater risks of recurrence. Such are the cancers arising in burn sears, vulval leucoplakia, chronic ulcers radiation dermatitis and other chronic inflammatory lesions, Bowen's epidermal careinoma in situ and the multiple squamous cell or basal cell growths in people with highly sensitive skins the extreme instance being the inherited disease xeroderma pigmentosum. In all of these cases, the surgeon knows that the risks of recurrence following extripation of established areas of growth are very great he less frequently recognizes clearly that the recurrences are due not to incomplete removal of tumour tissue but to fresh cancerous change in similarly predisposed tissue. If, then cancer appears in a burn sear or chronic ulcer, the entire searred or ulcerated area must be looked upon as a likely field of subsequent cancerous change and the proper surgery is not merely excision of the eancerous area, but extirpation of the entire prepared field—amputation if need be So also vulval leueoplakia which has commenced to become cancerous necessitates radical vulvectomy mere local removal of an area of growth is almost certain to be followed by recurrence elsewhere. The surgeon of course recognizes his limitations in cases of multiple skin cancer with recoderma pigmentosum or other highly sensitive skins, the only fully adequate surgery in such cases would be flaving

Mammary, surgers should take cognizance of the mode and extent of origin of mammary tumours. Since in many cases cancer of the breast arises not from a single minute focus but from a considerable field of predisposed mammary.

CHAPTER 8

STRUCTURE AND GROWTH OF TUMOURS

THE STRUCTURE and growth of particular kinds of tumours are described in the special chapters of Part II Certain general aspects of the subject however, require comment here For further details and references, see Nicholson's Tumour Studies my 1934 work, and the papers of Foulds and Cowdry

TUMOUR STRUCTURE AND FUNCTION

(1) The degree of organization of tumours

In Chapter 3 it has already been noted that most benign tumours show a high degree of differentiation and organization, and many malignant tumours incomplete differentiation or anaplasia but that some malignant tumours have a highly This last point deserves emphatic repetition The degree organized structure of differentiation and organization seen in many papillary carcinomas and adeno carcinomas approaches that of the normal tissues, and serial reconstructions of such tumours (references by Foulds) have shown that they have orderly patterns grow in obedience to rules which, in part, resemble those which regulate the growth of normal tissues" With the statement of Reimann and Toennies,

Benign growths have an organization, while malignant ones do not", surely no competent pathologist will agree

(2) Metaplasia in tumours

Tumour tissue probably never shows any peculiar metaplastic changes of which the parent normal tissue is incapable in non neoplastic lesions metaplasia in glandular carcinomas of the uterus (Fig 16), bronchi alimentary canal breast salivary glands or nasal cavity, has its parallel in similar meta plasta in inflammatory or hyperplastic states of these epithelia. The same applies to osseous or cartilaginous metaplasia, which is seen in reparative and inflammatory states of the mesenchymal soft tissues as well as in some of their tumours However in certain situations tumours are by far the most frequent pathological lesions to disclose the dormant metaplastic potentialities of the parent tissues Thus squamous metaplasia in the cpithelia of the gall bladder, pancreas, gastrointestinal tract or breast is very rare save in carcinomatous tumours although it has often been stated that squamous change commonly occurs in chronic bronchicctasis or bronchitis this is an error, except in carcinomas Mucus secreting squamous metaplasia in human bronchial disease is rare carcinomas of the breast (Fig. 17p) reveal a metaplastic potency of mammary epithelium which is rarely disclosed in any other lesion Goblet cell metaplasia has occasionally occurred even in carcinomas of the skin (Nicholson 1923) The difficult question of the histogenesis of many of the ovarian tumours involves consideration of the metaplastic potencies of the ovarian tissues-potencies which but for the existence of the tumours we would hardly suspect

by regenerative hyperplasia but tumour formation is rarely seen following the former and very frequently following the latter and on the clinical side while alcoholic eirrhosis seldom leads to henaue tumours the eirrhosis of haemochro matosis quite frequently does so. Of importance also is individual susceptibility of a particular tissue to tumour formation for example the epidermis of a person with recoderma pigmentosum or the intestinal mucosa of a person destined to develop familial polyposis is in an unstable state and is ready to become neoplastic on slight provocation. In such susceptible tissues it is probable that mild physical or chemical stimuli of diverse kinds insufficient to effect permanent changes in normal tissue, suffice to exoke persistent hyperplasia and eventual neoplasia

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this is seldom so great as to deprive the tumours wholly of recognizable resemblance to their parent, and a general preservation of type is usually apparent

(4) Structural variations in a single fumour

It is of great importance to recognize that, not only do different tumours in one class show individual differences of structure, but that a single tumour may show a great variety of structure. Thus a cancer of the breast may contain

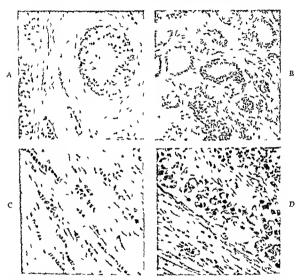


Fig. 17 —The range of structure in a carcinoma of the breast. A = intra duct carcinoma in large ducts (× 100). B = in small ducts (× 100). C = scirrhous spheroidal celled carcinoma (× 225). D = signet ring celled carcinoma (× 225).

areas of cribiform intra duct caromoma areas of papillary growth areas of infiltrating adenocarcinoma and areas of polyhedral-tell carcinoma partly of medullary and partly of scirihous type (Fig 17). A bronchial tumour may contain areas of adenocarcinoma mucoid curcinoma, squamous cell carcinoma and diffuse oat cell carcinoma. A thyroid tumour may display the whole gamut of possible structure, from perfectly differentiated thyroid vesicles, or

(3) Individuality in the structure of tumours

One of the most remarkable properties of tuniours is the stability of individual characters which they show Each tumour has its own peculiarities of structure and behaviour which it maintains largely unchanged even through a long and complicated metastatic career (Willis, 1934, Chapter 7) The same applies to transplantable animal tumours repeated serial transplants maintain, with minor viriations, the special characters of the parent tumours "Each tumour has specific properties, tumours owning the same parent tissue have family resemblances but individual peculiarities — All these properties are permanent and hereditary" (Foulds). This remarkable stability of individual type shows more clearly than any other single fact that neoplasia consists in an irreversible change in the tumour cells themselves and not in any adventitious change in their environment.



rio 16 —Squamous metapiasia in endometrial agenocarcinoma (× 120)

Minor variations of structure doubtless due to variations of available nutriment and other extrinsic factors, are seen in different parts of a tumour or in its metastases or transplants. Apart from mere degenerative changes these variations comprise increased or decreased structural differentiation as compared with the normal structure of the parent tumour Increased structural differentiation is exemplified by occasional instances in which a metastasis of an anaplastic epidermoid carcinoma may show well keratinized squamous-cell areas, or a metastasis of a cellular poorly differentiated carcinoma of the thyroid may show some typical colloid filled thyroid vesseles. Decreased structural differentiation is increased anaplasia is not unusual in metastatic growths. These often show greater mitotic activity than their parent primary tumour, especially in the liver (Willis 1932) with corresponding diminution of organized pattern. But

these features occur in some cellular carcinomas and teratomas. Even when a tumour has been correctly identified as epithelial, mistakes in diagnosis may be occasioned by mimicry of special appearances in the tumour tissue. Squamous cell or basal cell carcinoma may present pseudo glandular appearances (Fig. 19), thyroid vesicles may be simulated by glandular spaces filled with cosinophil secretion in glandular tumours of other organs, and fatty or glycogenic change in the cells of a carcinoma may cause it to simulate the appearance of renal carcinoma (Fig. 20)



Fig 18—Spindle-celled area of a lymph nodal metastasis of a squamous cell carcinoma of the tongue the fusiform tumour cells mingling diffusely with the fibroblastic stroma (× 82)



Ftg 19—Pseudo glandular appearance produced by desquamation and degeneration of the centres of the downgrowths of a squamous-cell carcinoma of the skin (×70)

(6) Secretory function in tumour cells

There is probably no glandular tissue endoctine or exocrine, the special secretion of which is not produced in some of its innocent or malgrant tumours Many examples of such secretory activities are referred to by Nicholson, Willis (1934) and Cowdry The most familiar instance of an exocrine secretion in tumours is the mucus produced so plentifully in the "colloid' or mucoid adeno carcinomas and less plentifully in the signet ring cell carcinomas and in the pleomorphic salivary tumours. The production of bile by carcinomas of the liver (references by Willis), and of digestive enzymes by carcinomas of the pancreas are also well known Mammary fibro adenomas may lactate (Nicholson Fig 2 Geschickter and Lewis) and this applies also to transplanted adenomas in lactating rats (Grauer and Robinson)

cystic areas filled with colloid to diffuse masses of cells indistinguishable from sarcoma. This structural heterogeneity does not conflict with the principle of tumour individuality enunciated above, the range of structure displayed by a particular tumour is itself one of its peculiarities.

The frequently variegated structure of individual tumours shows both the arbitrary nature of histological sub divisions of any single species of tumour and the pitfalls awaiting tumour graders. To set out, for example, to label all bronchial carcinomas subsets a supervision of the prefires or adjectives are merely descriptive of the possible variations of structure seen in tumours or in a tumour, of that species. Certainly in many tumours one or other variant predominates and it is legitimate to inquire whether predominance of particular variants has any bearing on prognosis. But certainly also, most such inquiries are vitiated from the outset because no exhaustive microscopical study of the tumours to ascertain their complete structural composition, has been or could be made. Hence, as already stressed in Chapter 3 ritempts at precise numerical griding of tumours for prognostic purposes are wasted effort.

(5) Mimicry in tumours

The structural versatility of cancerous epithelium pointed out by many workers (e.g. kettle. Cohn. Willis 1932 and 1934. Tudhope and Chisholm., Cappell., Saphir and Vass., Brooks) is not sufficiently appreciated by most pathologists Anaplasia metaplasia stromal reactions accompanying inflammatory changes adaptation to the architecture of invaded tissues—all these factors operate to disguise the epithelial nature of many carernomas and to simulate the structure of other kinds of timours (Fig. 18). It is still a prevalent habit to dub any highly cellular diffuse timour sarcoma, overlooking the obvious fact that any kind of timour when sufficiently maplasite and rapidly growing is diffusely and highly cellular. It is time too for pathologists to recognize that study of the fine relationships of stromal collagen or reticulin to the cells of anaplastic timours of doubtful nature will not enable careinomas sarcomas and other timours to be distinguished.

Some further specific warnings against possible histological misdingnoses may be mentioned briefly here. A cellular tumour containing scattered brown pigment is not necessarily a melanoma: it may be a carcinoma or some other growth with admired residues of former haemorthages. A cellular tumour with vacuolated fat laden cells is not necessarily a liposarcoma, it may be a carcinoma with some fatty degeneration of its cells or with many macrophinges laden with degeneration products. A highly vascular tumour with tumour cells lining blood filled spices is not necessarily an angioblastic tumour it may be an anaplastic vascular carcinoma or a vascular idenocarcinoma with haemorthage into glandular spaces. A tumour composed of spindle-cells and multinucleated guarit cells indiscriminately arranged is not necessarily a polymorphrus-celled sarcoma. These features are common in parts of anaplastic carcinomas. A tumour containing large irregular multinucleated syncytial masses associated with extensive areas of hiemorthage is not necessarily a chonon-epithelioma.

nucleols for many years, concluded (1936). "The nucleolus is much larger in proportion to the size of the nucleus in all malignant cells, regardless of the type or origin of the neoplasm, this difference being great enough to permit easy differentiation from all other cells in the hands of one experienced with fresh tissues" This conclusion is cited only as an example of the dangers of preoccupa tion with one small facet of a large problem. To any pathologist aware of the absence of sharp distinctions between benign and malignant tumours, of the gradual nature of the neoplastic change, and of the close resemblance of some well differentiated malignant tumours to the corresponding normal tissues both in general architecture and cellular details, such a conclusion will of course appear absurd Cowdry and Paletta measured the sizes of the cells, nuclei and nucleoli, in many experimental and human epidermal carcinomas, and found that, while many malignant cells showed a high nucleocytoplasmic ratio and large no single cellular measurement made yielded results so characteristic of malignant cells as to differentiate them invariably from neighboring hyperplastic epidermal cells

Nuclear hyperchromatism, though common in actively growing malignant tumours is not a constant or distinctive feature, and Feulgen's reaction shows that malignant cells do not differ significantly from normal cells in their thymonucleic acid content (Cowdry)

(2) Mitosis

The earlier studies of mitosis in tumours (Stroebe, 1890, Hansemann 1890 1892, Pianese, 1896, and others) have been well reviewed by Levine (1931) who has himself made a painstaking research into the chromosome counts and the abnormalities of mitosis in tumour cells The few mitotic figures seen in benign tumours usually appear normal but in rapidly growing malignant tumours many abnormalities of mitosis are observed. These include multipolar and abortive mitoses, variations in the size and number of the chromosomes, which may reach several hundred (Deckner), and are often approximately tetraploid or polyploid in number (Levine), delay and irregularity in the movements of the chromosomes and failure of cytoplasmic division, leading to multinucleated giant tumour cells Hansemann and others have seen in these abnormalities an essential feature of neoplastic growth but this view cannot be accepted, for, as Galeotti and others showed abnormal mitoses can be produced in growing or regenerating tissues by the application of heat or chemical agents, and they are also to be seen in regenerative hyperplasia. Hence, as Cowdry and others have insisted their presence in rapidly growing tumours in which of course degenerative changes are common, is not surprising

The a portion of tumour cells which are in mitosis at any given time is, in most cases a good measure of the rate of growth of the tumour Rapidly growing tumours may show mitosis in 5 per cent or more of their cells the proportion probably never exceeds 10 per cent. Although special fixatives are necessary for preservation of the finer deails of mitotic figures satisfactory pictures are often afforded by the ordinary horautoxylin stained paraffin section of formalin fixed tissue (Figs. 21 24). As long ago as 1890 Zenker remarked on the good preservation of flutotic figures in post mortem material and Evans (1926)

Secretion by tumours innocent or malignant of the endocrine glands is the cause of most of the hyperhormonal states e.g. aeromegally, hyperparathyroidsmadernal virilism hyperinsulinism and hyperaditualism and of some cases of hyperthyroidism. Granulosa cell tumours and arrhenoblastomas of the ovary produce oestrogenic and androgenic hormones, and interstitial-cell tumours of the testis may produce precocous puberty. Chorion-carcinomas or their metastases evoke the hormonal results of pregnancy including a strongly positive Zondek-Aschheim test, persistent decidual rection and luteal existe changes in the ovaries. The hormonal disturbances involved in the production of the positive pregnancy reactions accompanying some malignant tumours of the testis are in need of further elucidation.

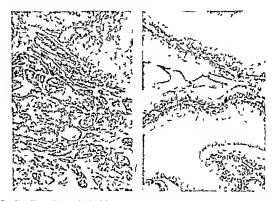


Fig. 20—Clear-celled pseudo glandular cystic structure in a glycogen rich epidermoid carcinoma of the skin of the neck in a woman aged 72 (see p. 200). A carly glycogenic change in cincerous clump s. If r cysts lined by taxers of clear cells and containing watery fluid zich in Plycogen (y 66).

THE CYTOLOGY OF TUNIQUES

(1) The nucleus

Some malignant tumours show many nuclear abnormalities including hyperchromatism grant nuclei lobed and multiple nuclei abnormally large nucleoi and abnormal intioses. Struck by these change, many workers have adopted the view that neoplastic must consist in some piculiar change in the nucleus or in mitosis and some finitastic hypotheses have been advanced (3 t. Chapter 11) Others have become obsessed with nuclear and nucleolar chaiges as a means of recognizing tumour cells. Thus MacCarty of the Mayo Chipte after studying host animals produce the appropriate tumours, and from these characteristic cultures can be obtained. Under suitable conditions the cells of various tumours maintain their individually peculiar characters without change for unlimited periods of cultivation. As Lewis insists, the behaviour of tumour cell cultures shows plainly that malignant cells are permanently altered cells, and that they maintain their altered characters "independently of the special environment or agents which induced them"

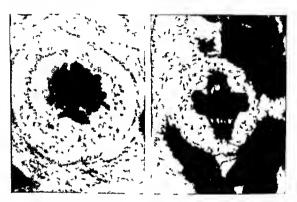


Fig. 22.—Enlarged views of mitoses from the same specimen as Fig. 21. A = late spireme or aster cut in equatorial plane B = aster figure with achromatic spindle and centrosomes $(\times 2125)$

THE STROMA OF TUMOURS

Only a bare outline of this subject can be given here, for further details, see Fischer, Bohmig and Chapter 10 of my 1934 work

(1) The blood vessels of tumours

These comprise pre existing vessels and newly formed vessels derived from them. As described in Chapter 9 pre existing arteries long remain intact in invaded tissues, but veins often suffer invasion and occlusion. In many tumours the formation of new vessels from residual ones is conspicuous. In projecting papillary of fungating growths the vascular channels must clearly all be newly formed by proliferation from the vessels of the subjacent tissues. But in many non protuberant tumours also as Goldmann (1907) showed by injection methods, there is an abundant proliferation of irregularly branching small vessels at the

showed that the number of mitotic figures suffers no appreciable decrease in specimens allowed to remain unfixed for 24 hours after excision

(3) The cytoplasm

No constant peculiarities of any of the visible constituents of the cytoplasm of tumour cells have been demonstrated Centrosomes Golga apparatus and mitochondria are present in mal gnant cells, and the variations in their appearance in some tumours are no more than might have been expected from the degrees of anaplasia or functional disturbances present (references by Cowdry)

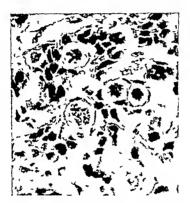


Fig. 21—From an hepatic metastasis of a careinoma of the tonsil showing numerous mitoses including multipolar mitoses and recently-divided paired and triple cells. (H.E. stained parallin section of formalin fixed in mitssue). (v. 600.)

(4) The tissue culture of tumours

The individual cytological peculiarities of tumours are often discernible in their cells when cultured in ittro and culture thus affords one important means of studying the eviology of tumours. Many studies have been made in this field foremost of which are those of Ludford and of Lewis, others will be referred to when describing the special kinds of tumours.

According to 1 cms the experienced eye can distinguish the cells of different tumours in culture from one another and from the corresponding normal cells but there is no one striking visible feature common to all malignant cells. Tumour cells in cultures show abnormalities of mitosis comparable with those seen in the tumours in viro. Inoculations from tumour cultures into homologous

irregular channels lined by endothehum only or by naked tumour cells. The vascularity of course varies greatly, from the nearly complete avascularity of densely scirrhous carcinomas to the extreme vascularity of such tumours as the pulsating skeletal metastases of carcinomas of the kidney or thyroid. Many tumours, as they grow peripherally, suffer central necrosis, because of inadequate vascularity or a suicidal occlusion of vessels.

(2) The fibroblastic stroma of tumours

Nearly all tumours, innocent or malignant, possess a connective tissue framework more or less appropriate to the parenchymatous tissue proper. Such stromal tissue is scanty and devoid of recognizable arrangement in many anaplastic carcinomas and sarcomas, moderate in amount and of orderly arrangement in well differentiated malignant and benign tumours, and abnormally abundant and dense in scirrhous carcinomas.

The architecture of the fibroblastic skeleton of tumours varies with the nature of the tumours and the nature of the invaded tissues. Many carcinomas are sharply alveolated or clumped in structure, compact masses of cpithelium being set in the spaces of a well defined stromal spongework. In many anaplastic growths, however, the distinction between tumour parenchyma and stroma is less clear, the tumour cells lose their polarity and the scanty residual stroma

is mingled with them in a diffuse and disorderly manner

Connective tissue is ubiquitous, and the fibroblastic proliferation (desmo plasia) evoked by a particular carcinoma is similar in most host tissues. Thus the metastases of a scirrhous carcinoma in different situations such as lung liver, bone marrow and lymph glands, will usually show approximately similar proportions of tumour cells and fibrous stroma—another instance of maintenance of individuality by tumours. Metastatic tumours in the brain, however, often contain less fibrous stroma than their fellow metastases elsewhere, probably because of the paucity of connective tissue in the central nervous system. Infiltrating tumours in the lung often use the alveolar walls as a preformed vascular stroma, and the tumour plugs occupying the air-sacs are themselves devoid of vessels or stroma (Fig. 42)

The elastic tissue of tumour stroma was studied particularly by Scheel Waljaschko and McConnell The elastic fibres in the walls of vessels and ducts long resist destruction by invading growths and can be demonstrated by appropriate stains after all other pre existing elements have disappeared Great proliferation of elastica occurs in the dermis beneath early carcinomas of the skin (see Fig 5) and underlying Paget's disease of the nipple and around main ducts in cancerous breasts (Sekiguch), Cheatle and Cutler, but there is usually little or no increase of elastic fibres in the stroma of invasive tumours.

incie of no increase of elastic fibres in the stroma of invasive tumour:

(3) The osteoblastic stroma of tumours

The reaction of bone to metastatic or invading neoplasms varies greatly In many cases the bone undergoes rarefaction and absorption but in others it becomes denser and heavier. This osteoplastic reaction occurs very frequently from carcinoma of the prostate $(\mathbf{q} \ \mathbf{v})$ less frequently from mammary carcinoma and relatively rarely from other carcinomas and, as suggested by Goetsch (1906)

margins of invading growths By injection methods also, Lewis found that each of several rat tumours had its own peculiar vascular pattern

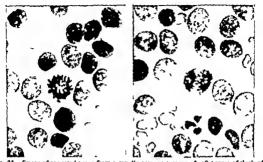


Fig. 23 —Smear of aspirated ussue from a rapidly growing timour of soft issues of thigh of a girl aged 16 years probably lymphosarcoma. A = an aster B = a diaster. The number of chromosomes which could almost be counted is normal or nearly normal. (x 800.)

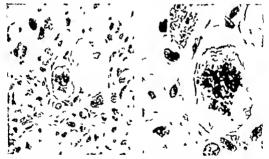


Fig. 4—Cellular pleemorphism and mitos s in an anaplastic tamour of the lung probably a fibrosarcoma. The enomeomes in the grint tumour cell could nearly be counted and even in the single section greatly exceeded the normal number. (* 300 and 800).

The new formed ressels in malignant tumours are usually small and simple in structure, and in rapidly growing tumours they consist of little more than

sometimes much wider. Astrocytic reaction is much more prominent in grey matter than in white, probably because protoplasmic astrocytes are more labile and responsive to stimulation than fibrillary astrocytes. The reaction zone about a metastatic growth has no "barrier" function, it is soon invaded and destroyed by the growth, while fresh reactive changes appear more peripherally. The astrocytes rarely survive for long in the substance of the growth. Oligodendrocytes appear to play little part in the reactionary ghosis around secondary tumours.

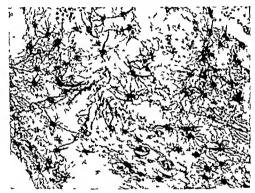


Fig. 26—Astrocytosis at the margin of a metastasis of mammary carcinoma in the brain (Cajal's gold-chloride sublimate) (× 150)

The reaction of non neoplastic neurogial cells to invading gliomas, and the persistence of such cells within the tumours, occasion great difficulties in the interpretation of the histogenesis of some of these growths (see Cox, Scherer, and Chapter 52)

(5) Leucocytic reactions excited by tumours

Excluding inflammatory infiltrates due to bacterial infections of tumours, collections of leucocytes of various kinds occur in or around malignant growths. Collections of limphocytes are often conspicuous around the invading margins of squamous cell carcinomas of the lip skin tongue, or cervix uter. The view, vigorodsly promulgated by Murphy and supported by Ewing, that this lymphocytic response is a specific defensive reaction against these tumours, has little to commend it (see Woglom 1929) Plasma cells often occur along with lymphocytes in the stroma of tumours and occasionally they predominate (Sormani, Willis) Neutrophil granulocytes often collect around necrotic foci in tumours and

and Axhausen (1909) it is probably evoked by diffusible chemical products of particular kinds of tumours. The fact that cancerous prostatic epithelium produces large amounts of an acid phosphatase suggests that the osteoplastic reaction of bone to intruding tumours is due to this or other enzymes liberated by the tumour cells

Another form of proliferative reaction of bone to secondary growths is the deposition of new bone by expanded periosteum. This may occur either as one or coarse regular or irregular trabeculae projecting vertically from it. Both kinds of formation are well seen in metastatic neuroblastoma in bone as described and depicted in Chapter 55, but similar new bone especially of coarsely irregular vertical arrangement may form also with many kinds of metistatic carcinoma, even tho e with predominantly osteoclastic results (Fig. 25A). This abundant new bone formation in secondary growths has often led to radiographic misdiagnoses of primary osteograpic sarcoma.



The 25—Skiagrams of bones containing metastases of carcinoma of the bladder (Care I Chapter 28). A = shum with metastasis containing much new formed periodical bone. B = seriebri which though full of metastasic growth shows normal structure—osteophyles at lower edge may have been evoked by the growth.

Another important fact for radiologists is that radiographically normal appearances may be seen in bones containing heavy metastatic growth (Fig. 2518). In such bone, the tumour infiltrates the marrow spaces only and leaves the trabeculae intact, there is neither osteoclasia nor osteoplasia.

(4) The neurnghal stroma of tumours

Metastatic growths in the brain often exerte a neuroglad proliferation the pain elements of which are the astrocytes' Special straining methods e.g. Cijal's Pidd-chloride sublimate method, are necessary to display this autrocytosis adequately (Fig. 26). The astrocytes multiply, become larger and their processes become correct and more numerous. The zone of reaction varies in width often it extends only 1 or 2 millimetres from the tumour margins but it is

as in Nicholson's and Schwenke's cases, must be taken into account in interpreting the structure of some supposedly "mixed" tumours of the uterus (see Chapter 48)

CARCINO SARCOMA

Good recent reviews and discussions of this controversial subject include those of Harvey and Hamilton Saphir and Vass, Foulds and Brooks 'Carcino sarcoma' implies either (a) simultaneous malignant neoplasia in two distinct tissues, an epithelial tissue and its non epithelial stroma, or (b) consequent sarcomatous change in the stroma of a carcinoma. The fortuitous development of two separate tumours a carcinoma and a sarcoma, in contiguity with each other is not relevant to the subject, and a "collision tumour" so formed should not be called a carcino sarcoma.

The evidence in support of the real existence of occasional carcino sarcomas is stronger in animal and experimental than in human pathology. The earlier experimental work which dealt with apparently sarcomatous changes taking place during successive passages of transplantable tumours, is well reviewed in the papers of Haaland (1908) and Russell (1910) Without discussing these controversial findings in any detail, I may point out that striking changes are known to occur in the histological structure of some tumours during serial transplantations, and that Lewis and Earle have found cyidence in tissue cultures of the structural versatility of carcinomas Thus Crocker tumour No 10, which was originally diagnosed as carcinoma and later assumed a sarcomatous appearance, Lewis believes may some day again be recognized as really a carcinoma So also, Walker rat tumour 315, originally diagnosed as adenocarcinoma, on serial transplantation assumed the appearance of a round cell sarcoma, yet Lewis says From the study of its malignant cells in cultures I am inclined to think that it is still a carcinoma." Earle described spindle celled transformation of a rat adenocarcinoma in transplants and cultures

Another and more recent kind of experimental evidence is the production by means of chemical carcinogens of tumours which have appeared to contain both carcinomatous and sarcomatous, constituents, such as those described by Bonser and Orr Since carcinogen, hydrocarbons can evoke tumours in both epithelial and non epithelial tissues, there is of course no intrinsic impossibility in simultaneous or nearly simultaneous neoplasia occurring in two distinct tissues exposed to such agents

But, before assuming that this has indeed occurred, it is essential to consider catefully whether the supposed 'sarcomatous' element may not be only diffusely growing epithelial tissue. Some spontaneously occurring numil tumours also show a seemingly composite carcino sarcomatous structure, and Rudduck and I have reported a canine thyroid tumour which seemed clearly to be of this nature. The primary growth in the thyroid showed a mixture of adenocarcinoma and osteogenic sarcoma, while metastases in the lungs consisted of sarcomatous tissue only, specifically identifiable because of its osteoid characters.

Human pathology affords at least one indubitable example of sarcomatous change in the previously benign connective tissue of an epithelial tumour, this occasionally occurs in a hammary fibro adenoma (Chapter 13) The case is somewhat peculiar, howeve, in two respects first, the connective tissue of a

especially in degenerating areas of mucord adenocarcinomas. They may invade, and be found within, large unhealthy tumour cells, a finding which has sometimes been interpreted wrongly as due to phagocytosis of the leucocytes by the tumour cells. Esimophil granulocytes are sometimes plentiful in and around tumours, and general cosinophila of the blood is present in some cases (references by Willis). The local and general cosinophil reactions of Hodgkin s disease are also to be noted here. The significance of such reactions in tumours is obscure the functions of cosinophil granulocytes are still unknown, and collections of these cells occur in many and diverse non neoplastic lesions. Macrophages Inden with lipiod material or pigment, are common in or around degenerating or haemorthagic tumours and foreign hads giant cells may also appear where lipiod absorption is in progress or where there are fragments of degenerating because or prescribe, hone.

(6) Metaplasia in the stroma of tumours

Osseous or cartilaginous metaplasia in the fibroblastic stroma of careinomas is not very uncommon. It has occurred with adenocarcinomas of the stomach (Gruber Laubmann), of the intestine (Foulerton, Clark) of the gall bladder (Micsch), of the uterus (Nicholson Schwenke), and of the salivary glands (q v) In Laubmann's case, metastases in the lungs showed osseous and earthliginous changes in the stroma, and in Micsch's case metastases in lymph clands liver and lungs, as well as the primary growth, showed plentiful strom; with many bony trabeculae containing bone marrow. In Schwenke's case there appeared to be a close relationship between the stromal ossification and squamous meta phasia in the tumour itself. Nicholson (1924) depicted ossification in the stroma of a careinoma of the prostate and the formation of nodules of hydrine cartilage. in the stroma of an adenocarcinoma of the endometrium. I have seen bony metaplasia of the stroma in a bronchial adenoma, and in a pleomorphic salivary tumour. Ossification or chondrification is well known in the fibrous component of mammary fibro-adenomas in dogs (Schlotthauer) and the same occurs occasionally in human mammary tumours (Cheatle and Cutler Tudhope) Foulds (1937) made a careful study of bony and cartilagmous metaplasia of the host tissues, induced by trinsplants of a fowl careinoma and pointed out the significance of this regarding the histogenesis of some supposedly mixed tumours

The occurrence of metaplasis in the stroma of prostatic carcinomia as in Nicholson's case, and of metaplasis growths as in Lauhmann's and Micech's cases points to the correct interpretation of a case described by Schmorl in 1908. This was one of prostatic circinoma with osteoplastic metaptases in many hones and metaptases in the lungs which showed osteo-chondro sarcomatous," tissue minefed with carcinoma. Schmorl believed that osteoplasis induced in the bones by the carcinoma had become surcomatous and that osteoprotrium in the fungs along with metaptatic circinoma, but a preferable interpretation is that osceous and cirtilaginous metaplasia took, place in the stroma of circinomations metaplasia.

The possibility of stromal chondrification or ossification in uterine carcinomas

of new fibres from damaged nerves in and around tumours, but without supposing

That denervation of a tissue may inhibit invasive tumour growth into it, was suggested by some observations of Cheatle's on the spread of rodent earch norms of the skin, and experimental work (references by Willis, 1934) suggests that the variations in rate of growth of tumours in tissues under different states of disturbed innervation may be due to vasomotor changes. Further work is needed on this subject.

RATE OF GROWTH OF TUMOURS, AND FACTORS AFFECTING IT

Different tumours differ very widely in their rates of growth. Many benign, and some miligiant tumours grow very slowly and attain only a small bulk after many years, some anaplastic tumours grow with mushroom like rapidity. I have examined a metastatic deposit of a bronelinal careinoma situated in the oral mucous membrane, which grow in 4 weeks from just visible dimensions to a projecting tumour 3 centimetres in diameter and 12 grammes in weight. I have also seen patients with metastatic growths in the liver, in whom the anterior edge of this organ was at pulpably lower levels on several days in succession. Eveleth and Vetzel reported a case in which following excision of the lung, recurrent growth into the open pleural cavity from a small residue in the bronehal stump was found at necropsy 58 days later to have attitude a weight of 2 500 grammes, a mean interess of 43 grammes daily. The authors estimated that, assuming the tumour to have grown regularly in an exponential manner, its final daily increase must have been 340 grammes, and that its rate of increase was of the same order as the maximal rate of early embryonic growth.

One of the individual characters of each tumour is its growth rate, which it tends to maintain nearly constant throughout its ericer. But many factors are known to be capable of modifying the standard growth rates of particular tumours. This is not surprising, for, as we have seen the high degree of structural and functional organization attained by many tumours shows that their growth is not wholly uncoordinated nor exempt from the influences governing the activities of normal tissues. Thus, tumours of tissues which are subject to hormonal control may also show evidence of similar control. As instances may be cited the acceleration of growth of carcinomas of the breast during late pregnancy and lactation and their retardation on cessation of lactation (Chapter 13) the retardation of some mammary carcinomas in mice during lactation (Haddow 1938), the temporary retrogression of some prostatic carcinomas following carcinomas following administration of oestrogens (Haddow et al., 1944).

The most remarkable instance of alteration of tumour growth rates effected by extrinsic chemical agents is the retardation of growth produced in both experimental and spontaneous tumours by carcinogenic agents (Haddow, 1938, Haddow and Robinson 1939, Badger et al., 1942) Pertinent here also are the occasional spontaneous retrogressions of malignant tumours some of which appear to have followed severe infections or major operations (references in Chapter 3). It is not improbable that when more is known of the chemical changes involved in carcinogenesis, in the hormonal control of both normal and neoplastic tissues, and

fibro adenoma is not a simple stroma in the tumour but has neoplastic qualities of its own ab inito, the benigh tumour being a genuinely mixed or composite one and accordity, sarcomatous change in this tumour is not accompanied by carcinomatous change in its epithelium so that the result is not a carcinosarcoma, but sarcoma supervening in a fibro adenoma.

With this peculiar exception and with the exception of the equally peculiar mixed tumours of the uterus I do not know of any reported instance in human pathology in which the interpretation of saccomious change in the stroma of an epithelial tumour is beyond doubt. Further of the many reported cases of carcino sarcoma accepted unreservedly. Even Harve, and Hamilton's well-considered and able advocacy of the reality of such tumours has failed to convince me. I believe that the structural vagaries of anaplastic and diffuse carcinomas and reactive changes in stromal tissues suffice to account for the appearances depicted by these and other writers. I do not deny that true carcino sarcomas may occur in human beings but no conclusively established case has been reported and most of the alleged instances are clearly only cases of pleomorphism in carcinomas.

most of the alleged instances are clearly only cases of pleomorphism in carcinomas. I am not alone in this sceptical attitude. Saphir and Vass reviewed 153 superior and vass reviewed 153 superior and vass reviewed 153 superior and vass reviewed 154 superior and vass reviewed 155 superior and vass reviewed a number of these tumors is very questionable. They also reviewed a number of their own tumours which were at first thought to be extended a number of their own tumours which were at first thought to be extended a number of their own tumours which were at first thought to be extended a number of their own tumours which were at first thought to be extended a number of their own tumours. Cappell described and depicted great pleomorphism in a prostatic carcinoma in which in some places the appearances were typically carcinomatious in others a sarcoma like structure was produced by diffuse growth of the carcinoma cells, while in yet other parts hyaline changes in the stroma produced superficial resemblances to cartilage and to osteoid tissue. Such appearances are readily misunderstood and in the past have given rise to much false interpretation as carcino-sarcoma' mixed tumours etc. The reader should recall also the paragraph earlier in this chapter on mimiery in tumours.

NERVES IN TUMOURS

In Chapter II of my 1934 work. I discussed in detail the relationships between tumours and nerves and concluded with Ludford Herzog and others that there is no satisfactory evidence that malignant tumour cells are innervated that all genuine nerves found in tumours are inclusions, and that supposed nerve endings in tumour cells depicted by several writers are only retraction bulbs or varieose nerve libres contiguous with the cells. Nerves show remarkable persistence in the substance of invading tumours so that all manner of relationships between residual nerve fibres and tumour elements will be demonstrable.

Moreover when a nerve trunk is damaged by a tumour numerous new fibrits grow from the living axis cylinders of the proximal stump of the nerve trunk. These new axis cylinders not only grow within the perincural tube of the proximal portion but penetrate into the neoplastic tissue. The process is exactly similar to what occurs after section of a peripheral nerve, and there seems no casion to suppose that the new formed axis cylinders exert any trophic influence on the neoplastic cells. (Rvire) Meissel also saw this regenerative outgrowth

as regards all of these substances, different workers have obtained very diverse results, no doubt because of differences in the nature of the tumours analysed and in the amount of the secondary changes present in the tissue. Voegtlin decided that "no conclusive evidence exists at present which reveals any quantitative difference in chemical composition between normal and malignant tissues. Whatever differences do exist are of a quantitative nature, the biological stemificance of which is difficult to evaluate.

(2) The carbohydrate metabolism and respiration of tumours

Warburg's early work in this field was summarized by him in 1925 and by Dickens in 1930. Warburg's technique permitted estimation of the tissue respiration (oxygen consumption) and glycolysis (the splitting of sugar into lactic acid) in thin slices of fresh tissue. He found that many normal tissues, especially actively proliferating ones, and also actively growing tumours, showed marked glycolytic activity under anaerobic conditions, that under aerobic conditions, the glycolytic function of normal tissues was suppressed in favour of oxidation, but that tumour tissue often showed aerobic glycolysis. A characteristic feature of the metabolism of tumour cells appeared to be their high power of glycolysis under aerobic as well as anaerobic conditions with low respiratory quotient, and this was attributed to some disorder of oxidation in the cells (Dodds)

Subsequent work, however, has shown that aerobic glycolysis is not peculiar to tumours, but is exhibited also by many normal tissues, e.g. testis, retina, tonsil, kidney meduilla, intestinal mucosa and bone marrow, and that some malignant tumours e.g. some human lymphosarcomis and mammary carcinomas, show low aerobic glycolysis. Interesting discussion of the pros and cons of the question will be found in the letters of Dickens, Boyland and others in Nature (1940), in which Berenblum et al. concluded that 'when a tumour is compared with the tissue from which it is derived, there are no characteristic differences or peculiarities between the carbohydrate metabolism of the two.' Orr and Stickland (1941), however found that in tumours arising in the rat's liver following administration of azo dyes there was a sudden change in metabolism as compared with that of the non-cancerous liver tissue.

It is clear that many actively growing tumours do show high aerobic and anae robic glycolysis and low RQ though these are not peculiar to tumours. The high aerobic production of lactic acid by some tumours has been shown in 1100, when fasting tumour bearing animals were given intraperitoneal injections of glucose, fructose or maltose, a striking decrease of pH values was shown by means of an electrode introduced into the tumours (Voegtlin). Fructose is said to be glycolysed by some tumours but not by others (references by Boyland)

(3) Constitutional metabolic effects of tumours

In Chapter 3 it was pointed out that eachexia accompanying malignant tumours is readily explicable as the result of ulceration, haemorrhage, pain and interference with important bodily functions, and that no specific cancerous poisons need be postulated. Study of the chemistry of tumours confirms this, no peculiar constituents or metabolites have been identified in tumours. Most of the labonous work done on the chemistry of the blood and other body fluds and tissues in cancer patients or tumour bearing animals has been wasted effort

in tumour metabolism these may all be seen to be related phenomena—and perhaps radiational carcinogenesis and radiational therapy may also be found to come within the same ambit. The hope of the therapist is that future research may discover some chemical substance or other agent capable of body wide application, which will be much more selectively lethal or inhibitory to tumour tissue than any yet known. If such a discovery is made, it will be as the result of more intimate probing of the chemistry of carcinogenesis tumour inhibition and hormone action.

THE CHEMICAL COMPOSITION AND METABOLISM OF TUMOURS

Although variable quantitative chemical and metabolic differences between some normal and neoplastic tissues have been detected it is doubtful whether these have any great significance as regards the nature and genesis of neoplasta. Only the barest outline of the main findings can be attempted here—for further details and references see the reviews of Boyland (1934). Holmes (1935), and Voegtlin (1937).

(1) The chemical composition of tumour tissue

A great deal of the work in this field is valueless because of unsuitably chosen material or lack of adequate normal controls. Tumours with abundant stroma or eich in blood or oedema fluid, or containing plentiful secretions or showing haemorrhages, degenerative changes or necrosis or recompanied by plentiful aggregations of inflammatory or phagocytic cells-all of these are clearly unsuitable for chemical analysis and comparison with normal tissues I ct very few recorded analyses make it clear that these sources of error were appreciated and avoided And how difficult it must be to word them will be recognized by every pathologist familiar with the diversity of microscopic structure and cellular health in malignant When he observes how frequent hoold degenerative changes and broad phagocytosis are an tumours when he knows that tumour cells commonly produce their appropriate secretions in great quantities when he sees the large amounts of glycogen of pigments of mucin or of calcific deposits present in certain tumours, he will attach little importance to the results of painstaking analyses of the cholesterol esters or enzymes or proteins or earbohydrates or inorganic salts of tumour tissues or to comparisons of these with analyses of the corresponding normal tissues. Further as regards most furnouse it is not possible to obtain the corresponding normal tissues for comparison normal tissues corresponding to carcinoma of the breast sarcoma of bone and ghoma of the brain are mammary epithelium osteoblasts and astrocytes respect ively and none of these can be obtained for analyses unmitted with other tissue elements except in the unnatural conditions of tissue cultures

With the foregoing points in mind it is not surprising to learn that several workers eited by Boyland and Voegtlin have found that many tumours have a relatively high lipoid content. that tumours differ in the amounts of sodium potassium calcium and magnesium which they contain but that there are no constant or significant peculiarities (Sherr), that various enzymes and aritamins glutathione pyrussic acid and mans other substances present in normal tissues are present also in tumours in satrable non-distinctive amounts. and that

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any abnormalities found have been no more than non specific secondary effects of the tumours. The hope that biochemical studies of the cancerous patient will reveal anything fundamental regarding the nature or growth of cancers or will lead to diagnostically useful tests, has so far proved a vain one, and is likely to remain so

Of the 30 or more tests which have been advanced for the chemo diagnosis of cancer reviewed by Panton (1937) and Woodhouse (1940) many have been patently absurd, and none has proved of any real use. To the pathologist, aware of the diversity of diseases included under the term cancer, the discovery of any generally applicable chemical 'test for cancer would indeed appear little short of miraculous. One might as well seek for a universal 'test for inflammatory diseases 11

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THE INVASIVE PROPERTIES OF TUMOUR CELLS

Properties of the tumour cell itself, known or hypothetical, which may be of significance as regards its invasive capacity include (1) its power of progressive multiplication, (2) its motility (3) its possible plingocytic powers, and (4) its possible elaboration of toxic or lytic substances. To these must be added another possible factor residing not in the tumour cell itself but in its environment namely (5) the possible loss of growth restraints normally exercised by neighbouring tissues on each other. Let us examine each of these in turn



Fig. 27—A metastasis of anaphastic carcinoma of parotid gland in lung showing compression of tung good demarcation of edge of growth but absence of a capsule (× 100)

(1) Progressive multiplication

Progressive multiplication of malignant tumour cells is certainly an important factor in their infiltrative growth. At the margins of an invading tumour successive generations of young cells are continuously budded out into the surrounding tissues and at the same time, expansive increase of the main mass of the growth must provide a vis a tergo which assists to thrust the budding marginal cells into all available crevices of the invaded tissues. The growth of the tumour thus resembles that of a root and its attriched rootlets, the main root enlarges expansively, while the rootlets and root hairs thrust their way along lines of least resist ance in the surrounding soil, and the growth and soil disrupting powers of the whole structure are attributable to the progressive proliferation of its cells

However, while proliferation is an important factor in invisive growth it is certainly not the only or even the most essential one. There are some rapidly proliferating tumours with no invasive properties such as the rapidly growing mammary fibro adenomas, and there are many carcinomas of relatively slow growth which are nevertheless highly infiltrative such as some scirrhous carcinomas of the breast or stomach. Further, the often rapid cellular multiplication of reparative and hyperplastic tissues or of transplanted embryo tissues, confers no invasive properties.

CHAPTER 9

THE DIRFCT SPREAD OF TUMOURS

IN CHAPTER 7 we saw how in the early development of a tumour, we must distinguish between spreading neoplastic change in a field of tissue and cellular proliferation of the neoplastic tissues. During the early growth of a tumour, these two distinct processes coexist but after the whole of the predisposed field has undergone neoplastic change the tumour grows solely by multiplication of its own cells. This proliferative growth continuously increasing the bulk of the tumour tissue, progresses in one or both of two ways with respect to neigh bouring normal tissues namely (1) expansive and (2) infiltrative.

(1) Growth by expansion

Growth by expansion, whereby a circumscribed tumour merely thrusts neighbouring tissues aside as it enlarges, calls for little detailed description. Purely expansive growth as with many kinds of benign tumours produces a sharply circumscribed tumour often distinctly eneapsulated. In malignant tumours all degrees of combination of expansive and infiltrative growth are seen—and when the former predominates, the tumour may appear to the naked eye to be sharply eircumscribed around most or all of its periphery as for example with many renal carcinomas. In such cases however, closer study usually reveals indistinct naked eye demarcation or microscopic degrees of infiltration at some part of the margin of the growth (Fig. 27).

While a tumour growing wholly or largely by expansion in a homogeneous tissue will usually be nearly spherical in shape one growing in heterogeneous issues or in situations where it is subjected to unequal pressures in different parts will be moulded into different shapes. Thus subcutaneous lipomas are usually more or less flattened because confined between the skin and the underlying parts, multiple uterine myomas suffer deformations by mutual compression circumscribed tumours projecting into hollow viscera often become elongated or otherwise moulded in shape by the cavities in which they grow and physically denote or rigid structures such as bones ligaments, tendons or stout visceral capsules confine and deform expanding tumours contiguous with them

(2) Growth by infiltration

Growth by infiltration, whereby the multiplying cells of a tumour insinuate themselves into the minute interstices of the normal tissues requires much more detailed description. We have to consider on the one hand the invasive properties of tumour cells and on the other hand the paths by which infiltration takes place and the changes brought about by such infiltration. Thus is the special subject of the present chapter. (For additional details see Chapter 10 of my 1934 work.)

(3) Phagocytic powers

The phagocytic powers of tumour cells, displayed for foreign particles by some kinds of motile cells in culture, are of little significance as regards the invasiveness of tumour. Steinhaus, Stroebe and others depicted appearances suggesting that tumour cells had engulfed blood corpuscles or stromal cells, but, as Greenough showed, most of the "eell inclusions" often seen in tumours are products of the cells themselves and not the remains of enclosed cells. Occasionally, polymorphonuclear leucocytes are found within tumour cells, I have seen this most frequently in mucoid circinomas, and it clearly denotes, not phagocytic ingestion of the leucocytes by the tumour cells, but invasion of deceneratine or unhealthy tumour cells by the leucocytes.

(4) Metabolites

Metabolites capable of affecting the surrounding tissues are undoubtedly produced by tumours The high factic acid output of rapidly growing tumours is well known and the stromal reactions evoked by invading tumours point to the influence of diffusible products of the tumour cells. According to Vocgtlin, "It is conceivable that the excessive amounts of lactic acid present in tumours with the consequent decrease in pH may be concerned in the destructive action of tumour cells on adjoining normal tissue' However, there is no evidence that slowly growing tumours show any significant metabolic differences from the corresponding normal tissues, or that any tumours produce abnormal metabolites with toxic or lytic properties. The degenerative and atrophic changes in the cells of tumour invaded tissues are readily accounted for as the result of mechanical pressure, vascular disturbances, and unsuccessful nutritive competition with the continuously multiplying invading cells. The idea that tumour invasion depends essentially on damaging effects exerted on the invaded tissues by soluble products of the tumour cells is entirely speculative

(5) Possible loss of growth restraints

Release from growth restraints was postulated by Ribbert as the essential factor in invasive malignant growth. Ribbert assumed that the capacity of most normal cells for indefinite multiplication was normally restrained by a complex set of factors largely dependent on the organized relations of the cells to adjacent tissues. Release from these restraints e.g. as the result of inflammatory isolation of groups of epithelial cells, permitted these cells to multiply continuously and to invade, thus forming a malignant tumour. Plausibility was lent to this view when tissue culture experiments not only proved the unlimited proliferative powers of normal cells but also showed the mutual organizing influence of epithelia and connective tissues when grown together.

However, while it is quite possible that in the early genesis of a pimary carcinoma connective tissue changes may play some part in facilitating epithelial invasion, there are good grounds for rejecting the hypothesis of impaired stromal restraints as an adequate general explanation of the prohierative and invasive properties of timours (a) The cells of a primary growth continue to invade neighbouring tissues to depths far beyond the extent of stromal changes due to the carcinogenic stimuli which evoked the growth (b) When transferred to

(2) Motility

The motility of ome kinds of tumour cells is well attested. Virchow (1863), Grohe (1865) and Carmalt (1872) long ago observed amoeboid movements of cells from freshly excised tumours, and Waldeyer (1872) and Vierth (1895) pointed out the possible importance of such motility in tumour infiltration and metastasis. While it is possible that these early workers mistook migrating macrophages for tumour cells, later tissue culture studies have shown that certain kinds of neoplastic cells can migrate. The earlier observations of Carrell and Burrows, Hanes and Lambert, and Lambert in this field have been confirmed by more recent workers, e.g. Lewis, Ludford, Cox and Cranage. Russell and Bland, and Coman.

Just as the most actively migratory cells in cultures of normal tissues are those of the microphage fibroblast series of mesenchymal tissues (Ludford) so also the most active motility observed in tumour cells is in those of mesenchymal tumours. Bland and Russell vividly described the movements of meningioma cells in cultures as follows. They glide forward like slugs training behind them a single triangular or tapiring process and throwing forth in front a number of mobile flame shaped processes which appear to be feeling their way through the medium. The chiracteristic form of migration is in the shape of a growing tongue or spike of cells which slip along one over another with their sides always in apposition each cell using the other as a scaffold along which to creep. Cinematography of the epithelioid shiets in both meningioma and foetal leptomeninges shows that the cells move about independently in them and crawl about on top of one another.

No doubt, in tumours derived from the normally migratory cells of the haemopoietic tissues free cell motility is commonly present, and this may easily be an important factor in the wide diffusion of malignant cells in the leukaemias and generalized lymphosarcomatosis

Active migration of the cells of gliomas of various types in tissue culture was described by Russell and Bland. Of tumour astrocytes they said, 'They are able as units to move freely in an amoeboid fashion and to regain their more elaborate form on coming to rest. These potentialities doubtless explain in some measure the highly infiltrative character of the ghomas.

The evidence for free cell motility in epithelial tumours however is inconclusive. Neoplastic like normal epithelia in culture, usually form compact sheets of cells from which isolated cells seldom migrate, and from the structure of well differentiated squamous-celled or glandular carcinomas, it also seems unlikely that they posses independent migratory cells. However, Coman (1942) observed that in tube cultures of some carcinomas cells implit become detached from the main mass, display amoeboid movement and form new isolated colonies. The same worker (1941) also advanced micro dissectional evidence that squimous carcinoma cells have subnormal adhesiveness, which might conceivably be related to their invasive properties. Further studies are needed to ascertain whether the poorly differentiated cells of anaplastic carcinomas may often be motile in fresh tissues or cultures.

the tout ensemble, different but more or less fixed for every type of managnant cell, that counts." It must be admitted, however, that so far the main components of the tout ensemble remain obscure

THE ROUTES OF INVASION

Infiltrating tumour cells take the following paths (1) tissue spaces, (2) intra cellular paths, (3) lymph vessels, (4) veins and capillaries, (5) arteries, (6) coclomic spaces, (7) cerebrospinal spaces, and (8) epithelial cavities



Fig. 29 —Interstitial infiltration of wall of a vein by spheroidal-cell carcinoma of breast (× 40)

(1) Infiltration of tissue spaces

Microscopically it is often clear that the cells of a tumour have infiltrated the tissue spaces or intercellular interstices dissecting the tissues apart along planes of anatomical cleavage and occupying all available nooks and crannies amongst the tissue elements. Tumour cells are seen in immediate contact with muscle fibres, parenchymatous epithelial cells, or nerve cells (Figs. 28, 29). This is indeed the initial and fundamental mode of infiltration, a carcinoma does not at once penetrate to the lumina of lymphatics and blood vessels, it must first infiltrate tissue interstices. So also the peripheral extension of well established growths continues to be parily or largely by a general infiltration of tissue spaces, not restricted to vascular channels or other preformed paths. This is not to deny that infiltration often involves lymphatics and blood vessels as well as general intercellular spaces, or that some tumours spread preferentially by vascular channels.

As might be expected, invasive growth progresses most rapidly in soft tissues with many potential or actual interstices, such as muscular tissue, the parenchyma of most viscera, central nervous tissue, or bone marrow On the other hand,

other sites and tissues of the body by metastasis the cancerous cells continue to display the invasive properties undiminished, properties which are not displayed by grafts of normal tissue experimentally transferred to the same sites (c) The unimpaired invasiveness of malignant tumours when transplanted from one animal to another shows that this cannot depend on any hypothetical loss of tissue restraints peculiar to the first animal (d) Tumours of identical origin show widely different invasive powers, and the particular degree of invasiveness displayed by a given tumour reappears repeatedly in its metastases and in the case of transplantable tumours, in repeated transplants Each tumour maintains its own peculiar inflitrative and metastatic proclivities (e) Pure cultures of cells in intro have clearly been removed from all restraints exercised by other tissues but, cultures of normal cells do not grow into tumours when implanted

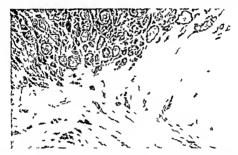


Fig. 28—Intersuital infiltration of muscular coat of small intestine by argentalfin carcinoma (\times 32)

into homologous animals while cultures of malignant cells of the same type produce tumours when implanted. It is clear then that the invasive properties of tumours reside largely or entirely in the tumour cells themselves. As Foulds said, 'There is no evidence that normal cells of any age have the capacity for behaving like cancer cells under any known conditions.

We must conclude them that the factors determining invasiveness in a tumour are still undetermined. Continued excessive proliferation is one of them but not the sole one. Mutual adhesiveness or possibly other physical properties, of the tumour cells may be concerned. Mothlity of tumour cells may play a part in some kinds of tumours. While diffusible metabolites from tumour cells may flay a part offect changes in neighbouring tissues, there are no solid grounds for regarding these changes as the essential prefude to invasion. Malignant invision cannot be explained as the result of release of restraints exercised by neighbouring tissues invasiveness is clearly a property of the tumour cell itself. Perhaps invasiveness does not depend on any single factor. perhaps as Cowdry concludes. It is

of the histological study of tumours Of the earlier accounts of this mode of spread, those of Waldeyer (1867), Hoggan (1878) and Reckinghausen (1885) are notable, while for clarity and completeness those of Heidenham (1889), Vogel (1891), Stiles (1899) and Ernst (1905) have not been bettered Handley (1922) attributed to lymphatic permeation an exaggerated pre eminence in tumour spread and metastasis which, though widely accepted in surgical teaching, is not endorsed by most pathologists (see Goldmann, 1911, Willis, 1934, and Gray, 1938)

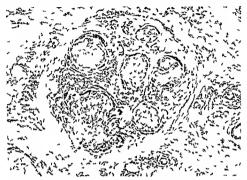


Fig. 31 —Permeation of perineural lymphatics by spheroidal cell carcinoma of breast (x 40)

Striking naked eye examples of lymphatic permeation are often to be seen in the serous membranes, the affected area presenting clearly visible white networks or strands of growth occupying and distending the subserous lymph vessels best specimens of this are seen in the visceral pleura in some cases of primary or secondary carcinom; of the lungs and in the mesentery in some cases of secondary peritoneal carcinosis. In most cases of this kind there is a coexisting permeation of the visceral lymphatics, e.g. extensive subpleural lymph vessel carcinosis of the lungs is always accompanied by widespread permeation of the peribronchial and septal lymphatics, often visible on the cut surface as fine nodular Such affection of the lung which is well described and branching strands depicted by Wu, is most often secondary to carcinoma of the stomach, but is seen also from carcinomas of the breast, uterus, intestine or lung itself Occasional cases of cutaneous melanoma display striking naked eve examples of lymphatic permeation, the affected vessels appearing as black cords between the primary growth and the regional lymph glands (Marchand, Handley, Hertzler and Gibson, Sutton and Mallia)

Microscopic examination of the infiltrating margins of carcinomas often reveals good examples of the growth of tumour cells along perineural perivascular

densely compact tissues with few interstices such as cartilage or dense fibrous tissue, act as more or less effective barriers to invading tumours. Thus tendons, ligaments, fasciae the selera strong visceral capsules periostea and articular and other eartilages often remain intact in invading tumours, or confine and mould them.

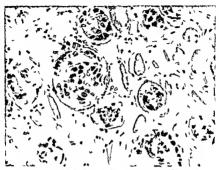


Fig. 30 -Invasion of skeletal muscle fibres by carcinoma of lung (× 280)

(2) Intracellular infiltration

Occasionally tumour cells are seen to have penetrated within the cytoplasm of the eils of the invaded tissues. Such intracellular invasion occurs most free quently into striated musele fibres and rarely into epithchal cells or nerve cells

Invasion of muscle fibres occurs usually along with interstitial infiltration but is sometimes the predominant mode of extension in the muscle. The malignant cells penetrate the sarcolemmal sheaths and multiply within the striated substance of the fibres. The sarcolemma long persists as a distended investing sheath for the cylinder of growth which has replaced the fibre substance. Often the cells advance axially along the fibre leaving a residual zone of muscle cytoplasm beneath the sarcolemma (Fig. 30). Examples of this mode of extension are recorded by Fujinami. Speed. Willis. Pulvertaft and Hartz and van der Sar.

Invasion of epithelial cells or of columns of cells is best exemplified in the extension of some secondary careinomas in adrenal cortical tissue (Willis 1934), rarely such invasion may be detected also in the liver or kidney

(3) Infiltration along lymph vessels lymphatic permeation

Lymphatics constitute a system of preformed paths of which many careinomas freely or even preferentially avail themselves. The part played by lymph vessels in the direct extension of careinomas was recognized almost from the beginning

of breast cancer with widespread permeation and skin nodules on the trunk, the cervical, axillary, inguinal, and often also the thoracic and abdominal lymph glands are cancerous, and extensive lymph vessel carcinosis of the pleura and lungs or of the pentioneum is always accompanied by involvement of the thoracic or abdominal lymph glands. Hence the absence of lymph nodal deposits in a region of secondary growths thought to have arisen as a result of lymphatic permeation is strong evidence that this interpretation is erroneous. This test proves for example, the falsity of the view of Handley, Kolodny and others that metastatic growths in bones arise by way of neighbouring lymphatics, for, as I pointed out in 1934 and as my subsequent observations confirm, most metastatic growths in the skeleton are not accompanied by tumour deposits in the regional lymph glands.



Fig. 33 -- Permeation of perineural lymphatics by adenocarcinoma of gall bladder (× 90)

The fate of cancerous lymphatics has been the subject of some debate. Handley described a perilymphatic fibrosis which obliterated the vessels and destroyed their tumour content so that the spreading permeation zone became separated from the parent primary growth by a widening zone of cancer free fibrosed tissue Along with Fitzwilliams, Fraser and most other workers, I have seen no evidence of such a process

Lymphatic permeation is not confined to small vessels, but occurs frequently also in vessels of large calibre such as the main tributaries of the cisterna chylindrand thoracic duct or the cisterna and duct itself. The earlier records of tumour invasion of the thoracic duct were collected by Leydhecker (1893). Winkler (1898) and Schwedenberg (1905), and in 1934 I fully reviewed the subject. The duct is invaded in about 3 per cent of all fatal cases of malignant disease, and in at least 6 per cent of all fatal cases of abdominal carcinomas. Invasion almost always takes place from tumour deposits in the upper retropentioneal lymph glands either directly or by way of the main lumbar or mesenteric tributaries of the cisterna. Carcinoma of the stomach is the responsible primary tumour in about one third of the cases, earcinoma of the uterus in about one quarter.

or interstitial lymphatics (Figs 31 34) In most cases such microscopic permeation extends only for short distances beyond the edges of the visible or palpable tumour, with some tumours however it is surprisingly extensive. Thus from a relatively small palpable growth in the breast, impalpably permeated lymphatics, perhaps indicated by scattered outcrop nodules in the skin, may ramify widely over the trunk and even on to the proximal parts of the limbs. Small gastire carcinomas may produce almost body wide permeation of lymphatics. I have seen a carcinoma of the parotid gland with permeation of the dermal and deep fascial lymphatics accompanied by outcrop nodules in the skin of the trunk and thighs (Case No VI, Chapter 17, and Willis 1934)

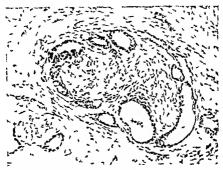


Fig. 32 -- Permeation of perincural lymphatics by adenocarcinoma of stomach (× 120)

However such extensive lymphatic permeation does not usually proceed in a simple centifugal manner from a single printry focus. In cases of manimaximationer with widespread permeation and skin nodules as also in my case of parotid cancer just cited, it is certain that tumour occlusion of regional lymph glands and man hymph vessels occasions repeated retrograde embolic dissemination of the tumour cells in plevus lymphatics thus establishing auxility foci and satellite nodules from which permeation extends to link up with other permeated areas. So also widespread permeation from gastric and other visceral growths proceeds not only from the primary tumours but from many metastatic foci established in lymph glands, pentoneum or other organs. Extensive lymphatic permeation is rately or never a simple centrifugal process but depends on confluence of separate zones of permeation from subsiditry foci established by metastasis

The condition of lymph glands in an area of presumed lymphatic permeation is of great significance. In a region of extensive permeation of lymph vessels it is clearly inevitable that all lymph glands in the region should be affected either by continuous permeation or by embolism. Experience confirms this in cases

The frequency with which gross tumour invasion of large veins is demonstrable at necropsy is insufficiently appreciated. In 500 consecutive necropsies on cases of malignant disease of all kinds (Willis, 1941), I found naked eye examples of invaded veins in 102 cases (20 per cent). This, of course, is a decided under estimate, since it was impracticable to make a complete dissection of all veins in affected areas. In a series of 64 necropsies on cases of epidermoid carcinoma of the head and neck, in which careful dissection of all main veins in this region were undertaken, these veins were found grossly invaded in 30 cases (46 per cent). A detailed account of the first 20 cases in this series was published in 1930.

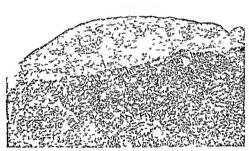


Fig. 35—A low mound of thrombus formed over area of invasion of lumen of a main hepatic vein by a metastasis of carcinoma of lung. The thrombus itself contains colonies of tumour cells (x 10)

In 1934, I collected from the literature examples of invasion of large veins by tumours of all kinds. Carcinomas of the stomach pancreas, liver, lung, thyroid and kidney often invade main veins, as do also embryonic renal tumours, testicular teratomas, chondrosarcom is and other sarcomas. The invading tumours some times grow along the lumen of the veins for surprising distances, e.g. renal carcinomas invading the renal veins may grow up the inferior vena cava and into the right chambers of the heart (references by Polayes and Taft), chondrosarcomas have extended in continuity through the vena cava and right cardiac chambers into the pulmonary arteries (Fry and Shattock, Kosa) and the same has been observed of testicular tumours. Probably the most extensive intravascular growth recorded was from the teratoma of the testis described by Herzog, this formed a continuous irregular cast occupying the vena cava renal veins right chambers of the heart, and the pulmonary arteries even to their peripheral branches.

The structural details of invasion of veins were first studied carefully by Goldmann and later by myself (1930 and 1934) Purely mural invasion of a large vein may set up a proliferative thickening of its intima which, along with mechanical

of the cases, while the remainder include carcinomas of the intestine, gall bladder ovary and other abdominal and pelvic viscera, and only occasionally pulmonary, ocsophageal or other growths affecting the duct in its thoracic part. The tumour may occupy and distend the duct in part or the whole of its course, and the cylindrical or fusiform mass of growth may attain a diameter of 1 or 2 centimetres.

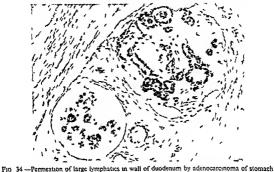


Fig. 34—Permeation of large lymphatics in wall of duodenum by adenocarcinoma of stomach (× 120)

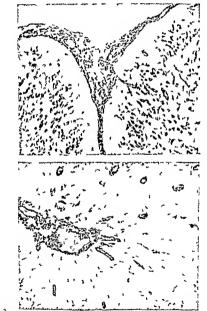
In other cases occluding masses of growth alternate with segments of patent duct or with masses of thrombosed lymph. Permeation frequently extends into the tributaries of the duct, and adjacent thoracie or cervical lymph glands are often affected so that the cancerous duct itself may be difficult to distinguish amidst irregular masses of growth. When the duct is affected throughout its whole length the tumour may project from it into the great veins in the neck. Cancerous occlusion of the thoracie duct is the most frequent cause of chylous assates, which however, is present in only a minority of cases of such occlusion. Chylo thorax may also be present. These chylous effusions probably result from obstructive ectasia and rupture of tributary lymphatics. (For a valuable review of chylous and pseudochylous effusions see Wallis and Scholberg.) The cancerous thoracie duct as a source of metastasis is discussed in the next chapter.

(4) Invasion of veins and capillary blood ressels

Infiltrating tumours frequently invade the walls of small or large veins, pene trate to their lumina and proliferate intravascularly. Certain classes of tumours, eg renal carcinoma, are notorious for their behaviour in this way and may extend continuously within large veins for great distances. It is however, important to recognize that venous invasion is not peculiar to any particular class of neo plasms, but is shown in greater or lesser degree by almost all kinds of malignant growths.

(8) Invasion of cpithelial cavities

Distension of the major hollow viscera by bulky growths within them and polypoid projection of the growths from orifices, as in the uterus, renal pelvis or alimentary canal, of course does not necessarily imply invasive growth Extension of malignant tumours within the cavities of main duets, however, is sometimes an important mode of spread. Thus carcinoma of the kidney or renal pelvis may grow down and distend the ureter and may even enter the bladder, uterine growths may extend back within the Fallopian tubes, nasopharyngeal tumours may grow along the Eustachan tube to the middle car



Figs 39 and $\frac{4}{3}$ —Invasion of the perivascular spaces of the brain by a diffuse tumour of the leptomeninges in a child (x 40)

The invasion of minute epithelial spaces sometimes plays an important part in the microscop e extension of tumours Infiltrating growths in the kidney may

compression of the vessel may result in its obliteration without either tumour invasion of the lumen or the formation of thrombus. Invasion of the lumen however, brings the tumour in contact with the blood stream. Over the invaded area of intima a small thrombus forms (Fig. 35). Organization and malignant infiltration of this initial thrombus follow the thrombus grows steadily until the lumen is occluded, when thrombussa along a section of the vessel takes place



Fig. 36—Section of a large thyroid vein invaded by a metastasts of renal carcinoma in the thyroid. The apparently detached clumps of tumour are cross sections of villiform fringes of growth which projected into the lumen. (× 60)

Malignant organization of this column of thrombus follows, and so the process advances section by section along the lumen of the occluded vessel. The relative rates of malignant invasion and organization of thrombus vary. Tumour cells may be found multiplying within unorganized clot. Sometimes masses or strands of naked tumour accompanied by little or no thrombus are seen projecting into the blood stream (Fig. 36). Some tumours, e.g. renal carcinoma commonly produce long cylinders of almost pure growth within the vun either occluding the vessel and adhering to its wall or more often leaving a narrow shit like channel cartring some blood flow.

We have been considering examples of tumour invasion of large vens. Even more frequent is microscopic penetration of capillaries and small vens in invaded itssues—a venous and capillary permeation comparable with that of small lymph atics described above (Fig. 37). Goldmain was the first worker to appreciate sufficiently the general importance of such permeation of blood vessels in the local extension of tumours and his findings can be confirmed by anyone who

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extend along the uninferous tubules, or in the testis along the seminiferous tubules or in the breast along the ducts. In making this interpretation in the breast great caution is essential, mammary carenoma is often of multicentric or even diffuse origin and what appears to be extension of tumour within a duct may

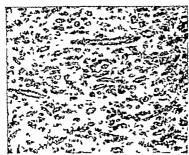


Fig. 41 -- From same specimen as Figs. 39 and 40 (× 40)



Fig. 42 —Intra alveolar spread of a metastasis of carcinoma of bladder in lung. (\times 80)

really be independent malignant change in that duct. A special instance of tumour spread in minute epithelial cavities is seen in lung tissue in which tumours often occupy the air sacs and spread from air sac to air sac ila the septal pores (Fig. 42).

CHAPTER 10

METASTASIS

The preformed paths along which tumours spread in continuity, as described in the previous chapter, are also the paths through which they metastasize by transport of detached tumour fragments to a distance. These paths are (i) lymph vessels (ii) blood vessels (iii) coelomic spaces, (iv) cerebrospinal spaces, and (v) cpithelial cavities. Metastasis by each of these paths will now be considered, further details will be found in my earlier work (Willis, 1934 and 1941)

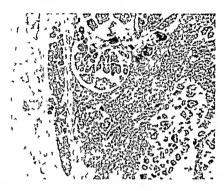


Fig. 43—Metastasis of papillary pairmo-carcinoma of ovary in a lymph gland. A large afferent lymphatic in the capsule and the subcapsular sinus are occupied by growth, which also extends deeper into the gland. (\times 60)

METASTASIS VIA LYMPH VESSELS

(1) The metastases of carcinomas in lymph glands

One of the most prominent features of the behaviour of carcinomas is thur feeding production of secondary growths in regional lymph glands. Most of these growths undoubtedly arise initially from detached tumour embolic carried to the glands in the lymph flow, and not by continuous permeation from the primary growths to the glands. Local recurrences following surgical removal of primary growths of the breast tongue lip vulva etc., occur either at the site of the primary growth or in the lymph glands and only rarely at intermediate sites. Many workers have carefully examined the trisues intervening between primary carcinomas and their early lymph nodal metastases, and have failed

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glands from various specific groups of carcinomas, see Willis (1934) and the appropriate later chapters of the present work

TABLE I

LYMPH NODAL METASTASES IN 426 CONSECUTIVE CARCINOVA NECROPSIES

| | P | ımary | - | No of cases | No with metastases in lymph glands | | | | | | | |
|------------------------------|-------|-------|-------|----------------|---------------------------------------|------|---|---|----------------|-----|-----|-------|
| Epidermoid | carcu | nomas | of th | e hea | d and | neck | _ | _ | | 64 | 51 | (80%) |
| Basal cell carcinoma of skin | | | | | | - | - | - | 5 | 0 | | |
| Oesophagus | - | | _ | - | | | - | - | ∸, | 17 | 12 | (71%) |
| Stomach | ~ | - | ~ | - | - | - | - | - | - ; | 85 | 76 | (89%) |
| Intestine | | - | - | _ | - | | - | - | - i | 65 | 20 | (31%) |
| Liver - | ~ | | - | | - | - | - | - | | .5 | 5 | |
| Biliary tract | - | | - | - | _ | - | - | - | - ' | 13 | 6 | |
| Pancreas | ~ | _ | _ | _ | - | | - | - | - | 11 | 8 | |
| Breast - | - | - | | - | | - | - | - | | 45 | 36 | (80%) |
| Uterus - | - | ~ | _ | ~ | _ | - | | _ | - | 30 | 15 | (50%) |
| Ovary - | - | _ | ** | - | - | - | - | - | - | 9 | 6 | |
| Prostate - | | | _ | _ | _ | - | ~ | - | - | 15 | 9 | |
| Kidney parei | ichvi | ma | ~ | - | ~ | - | - | _ | | 10 | 5 | |
| Kidney pelvi | | - | | | - | ~ | _ | - | - | 3 | 3 | |
| Bladder - | | ~ | - | _ | - | ~ | | - | | 5 | 2 | |
| Lung ~ | | ~ | _ | _ | _ | - | - | ~ | - | 27 | 25 | (93%) |
| Thyroid - | - | _ | ~ | - | - | _ | | - | _ | 6 | 5 | |
| Other sites | ~ | - | - | ~ | ~ | - | - | - | - 1 | 11 | 10 | |
| | | | | To | TAL | | | - | | 426 | 294 | (69%) |

(2) The metastases of non carcinomatous tumours in lymph glands

(a) Malignant growths of lymphoid tissue

These as might be expected, frequently produce secondary involvement of multiple glands. This applies to lymphosticomis reticulosarcomas, and their congeners lymphatic leukaemia and Hodgkins of slaesse. To what extent true embolic metastasis is responsible for the spread of these tumours from gland to gland is uncertuin. Metastasis certainly occurs but direct non embolic spread, and also spread of the neoplastic change itself to further areas of lymphoid tissue also take place.

(b) Other sarcomas

Excluding the matignant tumours of lymphoid tissue itself, sarcomatous secondary growths in lymph glands are rare. My series of 500 cancer necropieses (1941) included 18 sarcomas of non lymphoid tissues, and only 3 of these had metastasized in lymph glands. Warren and Meyer studied 237 non lymphoid sarcomas of which 17 (ie 7 per cent) were proved to have lymph nodal metastases. These comprised 12 cases of fibrosarcoma and also cases of osteosarcoma leiomyosarcoma and rhabdomyosarcoma. Other recorded examples of lymph nodal metastases from particular kmds of sarcomas will be referred to in the appropriate later chanters.

to find tumour in the connecting lymphatics (Heidenhain, Stiles Lengemann, Ewing, Willis, Long Gray) In a series of 40 specimens of carcinoma of the breast surgically removed by the radical method. I prepared microscopic sections from blocks of the pectoral muscles and fascia close to the tumours in the breasts, and found cancerous lymphatics in these sites in only 4 cases, in 2 of which there was grossly visible invasion of the muscle beneath the growth. I agree with Gray's conclusions that 'The spread of cancer cells by their growth as cords in the lumina of lymphatics is an unusual phenomenon in cases of operable cancer.

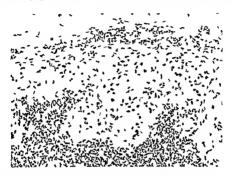


Fig. 44 —Metastatic signet ring-cell carcinoma of stomach in peripheral sinus of a lymph gland (× 150)

When it does occur such permeation seems to be generally only of microscopic extent. For operable cases of cancer embolism is the only important method (of lymphatic spread). In microscopic sections free tumour emboli are sometimes to be found in patent lymphatics (Willis 1934).

The afferent lymphatics of lymph glands open into the peripheral sinuses, in which, therefore early metastatic deposits are situated (Figs. 43–44). These channels are often to be seen distended by proliferating tumour cells which liter extend into the gland. Eventually the entire gland is replaced by tumour tissue which, however may long remain confined within the intact though distended capsule. Even in advanced cases with multiple glands affected it likely that embolism from gland to gland is largely responsible for the affected glands may at first be discrete and unconnected. Later however adjacent glands become bound together by tumour occluded lymphatics and infiltrated extra capsular tissues.

The accompanying Table I shows the frequency of lymph nodal metastases in the 426 consecutive necropsies on careinoma eases reported by me in 1941. For many references to other estimates of the frequency of metastases in 1941.

Lymphatic dissemination from the initially affected glands may become extensive, e.g. from the submental or submaxiliary glands to many lower cervical, axillary and mediastinal glands. Such extension from gland to gland is almost certainly embolic. Once a particular gland is heavily affected, cancerous occlusion of its main afferent and efferent vessels must lead to diversion of the lymph flow into collateral channels passing to neighbouring unaffected glands. These glands will now receive any emboli coming from the primary source as well as those from the initially affected gland. Every succeeding obstruction must result in further deviations of the lymph flow and further scattering of emboli over a wider and wider area.

A special instance of remote embolic spread from gland to gland is seen in cases of invasion of the cisterne chyli or thoracic duct from cancerous upper lumbar glands, accompanied by discrete metastases in the left supraclavicular glands.—Troisier's sign Most cases with cancerous duet show also cancerous left (and, less frequently right) supraclavicular glands. The mode of infestation of these glands varies. In some cases they are reached by direct extension from a totilly cancerous duet but in others the upper parts of the duet are patent and healthy and the cervical deposits are discrete metastases. In such cases we may suppose that tumour emboli borne in the sluggish lymph flow in the upper part of the duet are carried retrogradely into its jugular or other tributanes by respiratory retropulsions of the flow, or possibly that the emboli lodge behind the valves near the termination of the duet and establish small mural lesions whence infestation of the contiguous glands takes place

Haemic dissemination from cancerous lymph glands is also of frequent occur rence the tumour entering the blood-stream by direct invasion of neighbouring seins or ma the lymphatic tributaries of veins. Invasion of the main veins of the neck, in cases of eranio cervical carcinoma takes place usually not from the primary growths but from metastatic growths in the cervical lymph glands which lie in close contiguity with the jugular vein and its main tributaries (Willis, 1930, and see below). So also the iliae veins or inferior vena cava are readily invaded by metastatic growths in the pelvic and lumbar glands, the pulmonary veins or superior vena cava by deposits in the bronchial and mediastinal glands, and the portal vein or its main tributaries by deposits in mesenteric, peripancreatic or portal glands.

As regards haemic dissemination from lymph glands wa the lymphatic tribu taries of veins the most important instances of this are seen when the disternativation of the tributation of t

(6) Retrograde lymphatic embolism

We have already noted that cancerous replacement of a lymph gland or occlusion of a large lymphatic vessel must result in diversion of the lymph flow into collateral channels and that, as the cancerous affection of lymphatic pathways

(c) Melanomas

Melanomas whether of cutaneous or ocular origin frequently produce metas tases in lymph glands although hacmue distemination is often themore conspictious mode of metastasis. In some cases however, lymph nodal deposits appear very early or remain the predominant kind of metastases.

(d) Embryonic tumours of childhood

The embryonic tumours of childhood, especially neuroblastomas and nephro blastomas, often produce lymph nodal metastases

(e) Malignant teratomas

Malignant teratomas especially those of the testis, frequently metastisize to regional lymph glands and the metastases may be as complex in structure as the primary growth, or may be simpler

(3) Metastases in lymph glands from metastatic tumours in viscera

becondary as well as primary tumours produce regional lymphatic metastases. Metastatic growths in the lungs are often accompanied by deposits in the hilar and mediastinal lymph glands, metastases in the portal lymph glands commonly accompany heavy metastatic disease of the liver—secondary growths in the intestines are often accompanied by involvement of the corresponding mesenteric lymph glands. The distribution of metastatic lesions in many such cases makes it clear that the secondary visceral tumours were indeed the source of those in the neighbouring glands.

(4) Reactive changes in lymph glands

There has been some speculation as to whether pre metastatic changes obsurved in lymph glands have any special significance and whether lymph glands possess any protective or barrier? functions against tumours. Neither of these suggestions has any real evidential basis. The pre metastatic changes in glands adjacent to tumour areas consist of simple lymphoid and reticular proliferation and do not differ from the hyperplasias associated with many mild inflammatory states or with the absorption of extravasated blood or of degeneration products. The lymphoid hyperplasias associated with neighbouring tumours are readily explicable as due to mild bacterial infection in superficial growths to degenerative changes in the tumours or to blocking of ducts and retention of secretions in glandular organs. and no special cancerous nova need be invoked to explain them.

The supposition that tumour cells are destroyed or their multiplication suppressed in lymph glands is completely at variance with the facts. On the contrary for most carcinomas lymph glands appear to be highly favourable soils. Lymph nodal metastases are often of early appearance and rapid growth and histological study of early metastases fails to disclose any sign of wholesale destruction or arrest of growth of tumour cells (Zehnder, Goldmann 1907. Ewing, Willis 1934)

(5) Lymph nodal metastases as a source of further metastasis

Tumour deposits in lymph glands are often the source of further dissemination by the lymph stream or blood stream

In occasional cases with gross tumour invasion of systemic veins unattached tragments of growth have been found in the post-moriem clots in the right chambers of the heart (Weber Pitt, Griffiths, Geipel, Feinblatt)

The number of tumour emboli circulating in the blood stream must vary greatly from case to case and from time to time. Emboli liberated from small veins are probably few or solitary while gross invasion of large vessels or of the heart chimbers no doubt produces plentful emboli in repeated showers. In cases with widespread tumour deposits and multiple invasions of vessels in many different organs superimposed metastatic cycles must result in great complexity of the process of dissemination and often a high content of tumour particles in the circulating blood (Willis 1930 and 1934)

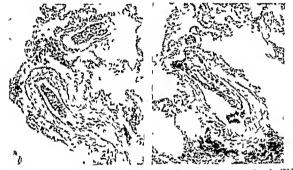


Fig. 46 - Tumour-emboli from carcinoma of bludder arrested in pulmonary arterioles. (> 120)

Several workers have claimed to have identified free isolated tumour cells in the blood before or after death (Marcus, Jonescu, Pool and Dunlop). Yet granting that some of these may have been genuine tumour cells it is nevertheless cert in that metastasis is attributable largely to the dissemination, not of isolated cells but of clumps of cells or masses of thrombus containing cells as already described. In the kukaemias however, we see the wholesale circulation of isolated tumour cells.

(3) The three main destinations of blood-borne emboli

Most tumour embol: consisting of fragments of tumour or tumour thrombus, must suffer arrest in the first arterioles or capillaries into which they are carried with certain exceptions to be considered presently, emboli liberated in systemic tens or in lymphatic tributaries of veins are arrested in the lungs, those liberated in the portal veins or significant the liver and those liberated in the pulmonary veins or left heart chambers in any peripheral organ or tissue to which they are carried in the systemic arterial blood

extends the available collateral routes must become very devious. Under these circumstances, reversals of flow must commonly occur and retrograde carriage of tumour emboli take place, as first stressed by von Reckinghausen. Vogel and Vierth. Retrograde lymphatic embolism explains such seeming anomalies as the metastasis of carcinomas of the tongue or pharynx to the contra lateral cervical lymph glands, or the occasional metastases of mammary carcinomas to the axiliary glands of the opposite side or to the inguinal glands. So also, carcinoma of the stomach or pancreas with deposits in the localea and upper lumbar glands is often accompanied by discrete deposits in the lower lumbar, itiac and even inguinal glands, these diminishing in size from above downwards. Doubtless the initial cancerous obstruction in the upper jumbar glands resulted in a retrograde flow of lymph in the lumbar chain of glands which therefore became cancerous step by step in craino caudal order. Similarly intra thoracic carcinomas with deposits in the mediastinal glands, often exhibit discrete deposits in the addominal and cervical glands, these diminishing in centrifugal order.

The most extreme alterations in lymph circulation occur when the cisterna chyli and thoracic duct are occluded. The lymph flow in both the rutroperitoneal and mediastinal tissues and in the abdominal and thoracic parietes is diverted into numerous collateral channels in many of which there must be reversal of the flow. It is therefore not surprising to find that cancerous disease of the thoracic duct or its main tributaries is usually accompanied by a wide dispersal of tumour deposits in the pelvic, inguinal cervical and avillary, as well as in the abdominal and thoracic groups of lymph nodes.

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Metastasis by retrograde lymphatic embolism is not restricted to lymph glands. Tumour emboli carried retrogradely in large lymphatics may suffer arrest in their peripheral pairower tributaries, and give rise to satellite growths around the main one. That this is the mode of development of satellite nodules in the skin around mammary and other growths is clear from the observations of many workers e.g. Winkler, Daus Haagensen and Stout. Crucerous permeation and occlusion of the deep dermal and fascial lymphatics in the neighbourhood of the main growth first occur. This results in deviations of the lymph flow in a centifugal often retrograde direction in the surrounding tissues whereby small detached emboli of tumour cells are carried into and arrested in the line superficial dermal lymphatics of the surrounding skin. Similar local retrograde dissemination in lymphatic channels plays an important part in the extension of some secondary growths in viscera e.g. in widespread lymph vessel carcinosis of the lungs heart liver or spleen following cancerous replacement of the regional lymph glands.

(7) Metastatic tumours in lymph glands masquerading as primary ones

Elsewhere (Willis 1934 Trinca and Willis, 1936) I have recorded many instances of secondary growths in lymph glands having been clinically mistaken for primary lesions. Large secondary growths in the cervical glands may be the first clinically evident result of an otherwise symptomics small primary carcinoma of the tonsil base of tongue pharyax oesophagus or lung or, as a precocious Troisier's sign of even a gastric or other abdominal carcinoma. Most if not all, so-called papilificrous lateral aberrant thyroids" are lymph nodal metastases

fibrous organization and it is clear that most of them grow promptly to form metastatic growths

(c) Arrest of tumour emboli in systemic arterioles or capillaries

As might be expected microscopic evidence of tumour embolism is to be found much less frequently in the systemic arterial system than in the lungs or liver For while the whole of the venous blood traverses the lungs, and the whole of the port il blood traverses the liver, only a fraction of the arterial blood traverses any given organ or tissue. However, recent tumour emboli within arterioles or capillaries have been seen in the heart, by Foot and co workers and by Morris in the kidneys by Eberth Winkler, Busse, Adams Froewis and Willis (1934) in the adrenals by Adams and Robson, in the spleen by Busse, Wegelin, Yokohata, Faulds and Mackay in bone marrow by Piney, and in the thyroid by Rice

(4) Unusual destinations of blood borne emboli

To the foregoing rules as to the usual sites of arrest of blood borne tumour emboli there are five possible or actual exceptions to consider, namely-(a) intracardul implantation, (b) retrograde venous embolism, (c) paradoxical or crossed embolism (d) transpulmonary passage of tumour cells, and (e) trans capillary passage of tumour cells in other organs

(a) Introcardial implantation

Fragments of growth carried in the systemic venous blood rarely become attached to the chordae or cusps of the tricuspid valve or to other parts of the endocardral surfaces of the right heart, and grow into branching or nodular masses within the chambers. This has occurred most frequently with teratomas of the testis (Kanthack and Pigg. Schmeel, Handfield-Jones Morgan), but also with alimentary and other eareinomas (Winter, Kaufmann, Nicholls, Culpepper and von Haam) Left sided endocardial implants from tumour fragments carried in the pulmon try veins are still rarer (Zenker, Kaufmann, Hunter) Branwood and Glazebrook saw a metastatic implant in an atheromatous patch in the root of the aorta

(b) Retrograde venous embolism

Retrograde venous embolism following occh, on of main veins with consequent reversals of flow, accounts for some pecul mestituated metastatic growths For ey invade and occlude the main example, should a carcinoma of the 1 left ovarian or testicular vein and renal vein, a retrograde flow takes p may easily be carried caudally pampiniform plexus, so that turned emboli al or spermatic cord metastases

and may establish isolated pelve the chief and or spermatic cord metastase. A similar mechanism accounts a chief of uterine chorion epithelmas in their vulva, broad ligament a capillaries into arts of the pelvis, and probably for sone is similarly situated second presently emboracterionmas of the uterus growths ver might arise from emborand those liber telly as the result of transent and others systic proposed that suggested that some metastate respirator art, retropulsion of blo serial organ or uss temie veins. Arnold, Erist eric veins are supposed that metastate respirators are systic supported this suggested. ren supposed that metastatic

(a) Arrest of emboli in the lungs

The occlusion of microscopic pulmonary arterioles by arrested tumour emboli first clearly described by Andree in 1874, and later by Zenker, Winkler, Schwedenberg Schmidt and others, can easily be verified by anyone who regularly examines sections of the lungs from cases of disseminated tumour (Fig. 46)

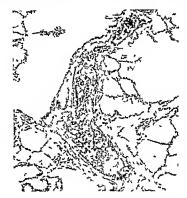


Fig. 47 — Tumour embolus from carcinoma of duodenum arrested within a pulmonary arteriole (\times 60)

These arrested emboli are to be found, not only in lungs containing obvious metastatic growths but also, as Schmidt and many subsequent workers have shown often in lungs devoid of visible metastases. In such cases, the arrested emboli show varying degrees of degeneration and of organization and fibrosis of accompanying thrombus proving their considerable duration yet their contained tumour cells have not proliferated or extended beyond the confines of the occluded arterioles (Fig. 47). These sterile or abortive tumour deposits show that metastass is more than embolism it includes also the growth of the embolic tumour cells at their site of lodgement.

(b) Arrest of portal embols in the liver

Arrested tumour emboli in small portal branch veins in the liver have been observed by many workers e.g. Waldeyer (1867). Rolleston Willis (1930 and 1934). These can be found in otherwise unaffected areas of liver as masses of tumour or of tumour and recently formed thrombus occluding veins, usually between 50μ and 500μ in diameter, in the small portal tracts. Unlike tumour emboli in the lungs those in the liver rarely show any signs of degeneration or

the lungs liver and bones, these contained discrete secondary growths in 29, 36 and 14 per cent of all fatal cases of malignant disease. If we exclude the 45 cases of tumours of kinds which never produce remote metastases, then the corresponding percentages are 32, 40 and 15 respectively. Or, if we consider only the 420 cases of carcinoma listed, 30 per cent had metastasized to the lungs, 41 per cent to the liver, and 14 per cent to the bones.

TABLE 31

SITUATIONS OF METASTATIC GROWTHS IN 500 CONSECUTIVE CANCER NECROPSIES

| | | NUMBER OF CASES WITH METASTASES IN | | | | | | | | | | | | | _ | | | | |
|--|---|---|--|----------------|--------------------|----------------|----------------|-------------------|----------------------|----------------|------------------|-----------------------|---|------------|-------------|---|---------|--------------|-----------------------------|
| Pr mary tumours | No of cases | Lungs | Liver | Вопея | Adrenals | N. dness | Braso | Heart | Thyroid | Ovanes | Pancreas | Spleen | Dura | Intestines | Skin | Mu cles | Stomach | Gall bladder | Other srtes |
| Carcinomas Epidermoid carcinoma of head and neck - Octoophagus - Stomach Stomach Bulary treet and liver Pannetas - Breast - Uterus - Ovaneta - Tomach - Tom | 64 17 85 65 18 11 45 30 9 15 10 27 | 19 3 1) 8 3 2 28 6 2 6 8 9 6 9 | 14 7 39 33 8 22 6 1 3 5 15 10 | 51612211 34832 | 5 43 1-9 1 1-25 23 | 81 32 71 14432 | 1211 177 137 1 | 4 12 1 122-1 1222 | 3 1 1 1 1 8 1 1 32 1 | 11621-3-111211 | 21 11 13 11 1221 | 2 1 4 7 7 3 | 7 | | 111-1111111 | 2 = = = = = = = = = = = = = = = = = = = | | -1211111117 | - 1 - 1 - 1 - 1 - 1 - 2 - 1 |
| Sarcomas | 26 4 5 | 11 3 5 | 2 2 3 | 6 1 2 | 3 | 1 2 | 1 2 | 1 | 1 | Ξ | 1 - | = | = | 1 | 1 | = | = | = | ī - |
| Totals Percentages of total | 500 100 | 147 29 | 180 36 | 68 14 | 45 9 | 38 | 29 6 | 24 5 | 21 4 | 16 3 | 15 3 | 14 | 13 3 | 9 | 7 | 4 | 2 | 2 | 8 |

(6) Tissues as soils for blood borne metastases

Elsewhere (1934) I have discussed in some detail the many peculiarities of distribution of metastatic tumours and the reasons for rejecting Ewing's opinion that the mechanism of the circulation will doubtless explain most of these peculiarities." Stephen Paget (1889) was one of the first to be struck by the discrepancies in the relative frequencies of metastatic growths in various organs and by the peculiarly selective distribution of the metastases of tumours of certain kinds and to liken tumour emboli to seeds' falling in 'soils' of different degrees of fertility. Many later workers have expressed similar views, and have concluded that different chemical or other factors in various tissues must determine whether or not arrested tumour particles shall germinate to produce secondary growths.

We have already encountered direct evidence of the truth of the "seed soil" relationship in tumour metastasis. We have seen that some tumour emboli arrested in the lungs fail to grow there, but remain infertile within the occluded

growths in the spleen could arise by retrograde carriage of tumour emboli from the liver in the portal and splenic veins. Elsewhere (1934) I have given reasons for rejecting this view. all alleged instances of tumour embolism in unobstructed large veins are open to other and preferable interpretations.

(c) Paradoxical or crossed embolism

Paradoxical or crossed embolism i.e. systemic arterial embolism by particles liberated in systemic tens but avoiding the lungs by traversing a patent foramen ovale must be admitted as a theoretical possibility but is certainly a rare and unimportant event in the dissemination of tumours. Thompson and Evans, reviewing the whole subject rightly concluded that claims for tumour metastasis by crossed embolism can be sustained only when careful microscopic study has proved the lungs to be free of growth, and none of the reported cases fulfils this requirement

(d) Tronspulmonary passage of isolated tumour cells

This has often been assumed to explain cases of tumour dissemination in systemic viscera without visible affection of the lungs. As with claims for paradoxical embolism, however so also those for unarrested passage of cells through the pulmonary capillaries can only be entertained when painstaking study has proved the absence of microscopic metastases and of arrested tumour emboli, in the pulmonary arterioles, and such proof has not been advanced. In view of what was said above regarding the usual sizes of blood borne tumour emboli, it is certain that wide tumour dissemination with seemingly unaffected lungs is much more often to be attributed to abortive tumour embolism in these organs than to unarrested traversal of them by single tumour cells

(e) Traversal of systemic capillaries by tumour cells

It has been suggested that traversal of systemic capillaries by tumour cells accounts for the relative immunity of certain contractile organs such as muscles, myocardium visceral muscle coats and the spleen, from tumour metastasis the implication being that isolated tumour cells are massaged through the capillary channels into the veins. However, since many tumour cells are too large to traverse capillaries and since most tumour emboli consist not of single cells but of considerable aggregates it is certain that the vast majority of such emboli must suffer arrest in the arterioles or capillaries of any tissue. What has just been said of supposed transcapillary passage in the lungs applies mutatis mutandis to that in other tissues.

(5) The frequency of blood borne metastases in various sites

For a detailed account of the pathology of secondary tumours in particular organs the reader must consult Part II of my 1934 work. Table II shows the frequency of true metastatic tumours in various sites in 500 consecutive necropsies on cases of miliginant disease (Willis 1941) all of the growths listed except those in the ovaries were discrete blood borne metastases cases of direct invasion of the organs being excluded. The three most frequent sites of metastases were

The precise chemical, enzymic or other factors involved in the successful growth or failure of transported tumour cells are still unknown. But light will be shed on the problem by future researches in the metabolism of normal tissues and of tumours, by tissue culture studies, and by the prosecution of studies like those suggested by Burrows in his excellent book, "Some Factors in the Localization of Disease in the Body"

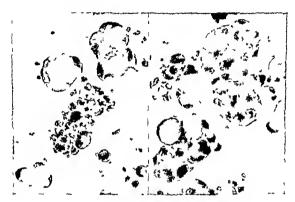


Fig. 48 -Clumps of signet ring tumour cells in pleural fluid from carcinoma of lung. (× 400)

TRANSCOELOMIC METASTASIS

In the development of widespread carcinomatosis of serous membranes liberation of detached tumour cells or larger fragments into the serous cavity and implantation of these on other parts of its surfaces play the main part, and permeation and metastasis in the subserous lymphatic plexuses only a subsidiary part. Useful accounts include those of Fiddes and McLean, Sampson, and Willis (1934)

(1) The entry of tumours into coelomic eavities

The site of entry of tumour cells into a serious cavity is often plainly apparent, as in many cases of papilliferous ovaring growths, or of gastrie or intestinal carcinomas especially those of the gelatinous type. Tumours of the uterus, bladder, provide, pancreas or kidney seldom disseminate in the peritoneal cavity unless the primary growths or their metastases in lymph glands have extended to the peritoneal surface. Pleural carcinomatosis follows primary or secondary growths in the lung only when these have involved the pleural surfaces. Pencardial

arterioles and undergo degeneration and fibrous organization. In the liver on the contrary, abortive tumour embols are rarely or never encountered. Lives the interest is clearly a favourable soil for the germination of most kinds of tumour embols, while lung tissue is not infrequently an unfavourable soil. Confirmation of this is afforded by study of the mitotic activity of metastatic tumours metasces of a particular tumour in different situations show great differences of mitosis, and the mitotic activity of hepatic metastases usually exceeds that of the primary growth and of secondary growths elsewhere, sometimes five fold or ten fold (Willis, 1932).

The absence of microscopic evidence of abortive tumour embolism in the liver and the high mitotic activity of hepatic metastatic growths no less than the great frequency size and number of such growths, show clearly that hepatic tissue is a fertile soil for tumour growth. In 1907 Bland Sutton suggested that this might be due to the high nutritive qualities of the portal blood and the abundance of stored glycogen in the liver later (1934), in the light of Warburg's work. I amplified this idea by suggesting that the poor oxygenation of the liver as well as its high earbohydrate content might favour tumour growth int. Haddow (1934), however, reviewing this question, thought it not unlikely that a more specific mechanism is involved, and that the liver is the source of a growth promoting substance of paramount importance, in the division of both normal and malamant cells.

In contrast with the liver, skeletal muscular tissue is clearly an unfavourable soil for the germination of disseminated tumours. In spite of a very large, aggre gate blood supply which must bring to the muscles a correspondingly large share of the tumour emboli distributed by the arterial blood, this tissue is a rare site of metastatic growths, as indeed of metastatic lessons generally, including infections. There is nothing peculiar in the riteriolar and capillary circulation in muscle to account for this relative immunity, we are obliged to seek the explanation in the peculiar metribolism of muscular tissue, in which it may be noted lactic acid—also an important product of many tumour cells—plays a prominent part.

The contrasting properties of various tissues as soils for embolic tumour cells must depend largely on metabolic differences relevant to the requirements of these cells Doubtless different kinds of tumours display different metastatic distributions because they have different metabolic requirements. Tissue-culture work shows the importance of the chemical environment for the survival and growth of cells of different kinds. Food substances oxygen supply hydrogen ion concentration and special growth promoting substances (trephones) all play a part in influencing the vigour of cultures. The condition of tumour cells in detached emboli or embedded in unorganized thrombus resembles that of a the nutritive and other requirements of the cells must be supplied tissue culture by simple diffusion. Hence just as in artificial cultures, the success or failure of embolically transplanted tumour fragments must depend on the chemical suitability or otherwise of their new environment. The eritical period for disseminated tumour cells must be that immediately following their embolic lodgement before they have achieved any stromal connexions with the surrounding host tissues, and while they are wholly dependent for their nutrition on diffusion from these tissues. Adverse chemical factors at this stage must be a major cause of abortive tumour embolism

cells in ascitic fluid during life. The healthy appearance of many of the cells in cancerous effusions, and the presence of mitotic figures in them (Fig. 49), accord with their ready powers of establishing metastatic implants. Some animal tumours which grow prolifically in the peritoneal cavity are easily transferable to other animals by intraperitoneal inoculations with either minced tumour tissue or ascitic fluid containing tumour cells.

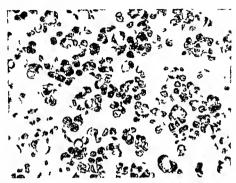


Fig. 50—A heavy deposit of signet ring carcinoma cells in ascitic fluid from a woman aged 45 with palpable abdominal turnours possibly of gastric origin (× 300)

(3) The histology of implantation

Misumi, Sampson and others have described the implantation and early growth of transcoelomic metastases. Following deposition of a clump of tumour cells on the serous surface, mild reactionary changes take place in the subjacent tissues, and a fibrinous exudate appears on the surface around the tumour cells. Organization of the fibrin follows proliferating vessels and fibrioblasts grow into it from the subserous tissues and convert it into a true stroma for the proliferating tumour cells. They begin to infiltrate the underlying tissues and the young metastasis is established. Sometimes the tumour cells grow over the serous surface in characteristic epithelial arrangement, and if they are mucus secreting cells, they often discharge their secretion directly into the serous cavity. (For illustrations of these changes see Sampson's excellent papers.)

(4) The distribution of transcoelomic metastases

(a) In the peritoneal cavity

Doubtless owing to the effect of gravity in the usual erect or semi recumbent postures, the earliest or most abundant tumour deposits are often found in the pelvis, especially in the rectio vesical or rectio utenne pouch. Another frequent

implants are rarely seen unless the parietal pericardium has suffered obvious invasion from without

In occasional cases of nodular sowing in a serious cavity, no obvious source of this is to be found, and we must admit that the infestation may have taken place from inconspicuous lymphatic extensions of growth. This is not surprising for even a small single inoculum of tumour cells might suffice to initiate wide spread coelonic dissemination the initial implant yielding successive secondary implants. In breast carcinoma, Handley (1922) attributed special importance to inconspicuous extensions of growth through the parietes from the deep fascial lymphatic plexus to the subserious plexuses and believed this to be the usual route of extension to both the serious cavities and the viscera. Others however, including Cheatle and Cutter Gray, and myself, have failed to find any evidence in favour of this view.



Fig. 49—Clumps of tumour cells in pleural fluid from woman aged 60 with presumed carcinoma of lung M=a cell in mitosis V=a vesicle of tumour cells (\times 300)

(2) Free tumour particles in scrous cavities

Many workers have seen free tumour cells or cell aggregates in the effusions accompanying peritoneal or pleural earcmomatosis (Beneke Pusinelli and Geipel Gwyn Ssobolew Josefson Jacobsthal Kaufmann Zemansky Sampson, Karp, Graham, and de Vries) Josefson was the first to search for tumour fragments in stained sections of the centrifuged deposit a technique which was used also by Zemansky, Karp and Graham and which facilitates identification of tumour cells in fully one half of the cases of effusions due to tumours (Figs 48 50). The tumour cells may show mitothe figures. Glandular tumours are often recognizable by the presence of signet ring cells or of complete glandular acini or vesicles free floating carcinomatous vesicles first described by Beneke have also been recorded by Graham and de Vries. Hickling described the vital staining of tumour

(b) Adhesions

Adhesions frequently accompany tumours in the scrous crivities. They may become very extensive, binding the viscera into an inseparable scirrhous mass in which it is impossible to distinguish transcoelomic dissemination from diffuse infiltration of tissues. Caremomas of the stomach and breast are the most prone to produce diffuse adhesive disease of this kind.

(c) Accumulation of mucus

In the serous cavity accumulation of mucus often results from massive or disseminated mucoid adenocaremomas ("colloid cancer"), good accounts of which were given by McCrae and Coplin, and Roth When carcinomatous tumours discharge large quantities of mucus into the peritoneal cavity, the result is identical with that of 'pseudomyxoma peritoner", a term first applied by Werth (1884) to massive gelatinous accumulations resulting from perforated pseudomucinous cystadenomas of the ovary

(6) Secondary tumours in serous cavities masquerading as primary ones

Clinical misdiagnoses may be caused by the coelomic metastases of otherwise symptomiess primary growths elsewhere. Many cases have occurred in which the pelvic deposits of gastric or other abdominal careinomas have been mistaken for primary carcinomas of the rectum (Toyosumi, Dann, Wakasugi, Boas Anson) Even mammary circinoma may be overlooked while producing its main symptoms by its coolomic deposits, this had happened in one of my necropsy cases, in which peritoneal metastases had led to a diagnosis of "cholecystitis". The frequent simulation of primary by secondary growths in the ovaries is well known

Pathological misdiagnoses of primary endotheliomas ' or "mesotheliomas of serous membranes have frequently been made in cases of secondary disease from unrecognized primary growths elsewhere. In 1934 I reviewed many reported cases of supposedly primary neoplasms of scrous membranes and concluded that most, if not all of them were only examples of serosal disease secondary to undiscovered tumours, usually in neighbouring viscera. My perusal of the more recent literature and my own later experience have confirmed that opinion I find accounts like those of Wells (1935) and of Yoshida (1937), of serosal 'papilloma incomplete and unconvincing Wells failed to examine microscopically an enlarged prostate, or to mention the pancreas and thyroid, or to indicate how thorough his examin ition of the bronchi and alimentary tract had been, and Yoshida s report suffers from similar omissions Gomori s diagnosis (1936) of "peritoneal mesothelioma' made from a biopsy specimen removed during laparotomy on a man of 49, who had had gastric symptoms for 9 months and in whom a skiagram had shown a pre pyloric filling defect diagnosed as carcinoma needs no further comment None of Geschickter's large collection (1936) of supposed mesothelial tumours" of serous membranes is adequately reported In Fahr s 7 cases (1935) of "fibro endotheliosis" of the pleura the necropsy accounts are incomplete, and the figures more than confirm Fahr's opinion that the tumours 'resembled" carcinomas Scheidegger (1935) properly identified as carcinomas 4 tumours which involved the pleura diffusely, but his suggestion

site is along the attrichment of the mesentery to the small intestine, probably because the many small recesses alongside the entering mesenteric vessels favour the lodgement of tumour particles. The omentum and epiploic appendices are often heavily infested, and in some cases especially of upper abdominal care nomas, the most numerous nodules are found on the undersurface of the diaphragm, particularly on the right side. No part of the peritoneal surfaces is exempt, and in advanced disease heavy confluent tumour deposits are almost universally present.

Transperitoneal deposits may affect hernial sacs, as described by Rolleston and by Satke and Salzer, and as in the following four personally observed examples

- Male 47 Anaplastic carcinoma of liver metastases in fundus of inguinal hernial sac found at necropsy (Willis 1934)
- (ii) Male 68 Squamous-cell carcinoma of tonsil with widespread metastases contents of bilateral inguinal herriae found at necropsy to be infiltrated by growth (Willis 1941)
- (iii) Male 46 At operation for repair of a long standing inguinal hernia which had recently become painful sac was found to have nodular thickened walls which microscopically showed spheroidal-cell careinoma. Recent indigestion suggested gastine careinoma (Trinça and Willis)
- (iv) Male 62 Recent discomfort had been noticed in long standing biliteral inguinat hemise. Patient was admitted urgently to hospital because of an attack of somiting thought to be due to obstruction but hemise were reducible. Lapitotomy disclosed carenoms of stomach with peritoneal metastases. Necropsy verified this and showed deposits of growth in both hemal sacs.

Transcoolomic metastasis is responsible for most secondary growths in the ovaries which are discussed in relevant chapters of Part II

(b) In the pleural cavity

In the picural envity transplanted tumour nodules may be found in all parts but are often most abundant in the eosto phrenic recesses on the surface of the displirigm or along the paravertebral gutters

(c) In the pericerdial eavity

In the pericardial eavity discrete nodular transplants are not common and they must be distinguished from nodules springing from secondary growths permeating the epicardial lymphatics

(5) Results of secondars tumours of serous membranes

(a) Iffusions

Effusions serous or hiemorrhagie are frequent resulting partly from cancerous occlusion of lymphatics and veins and pirtly from irritative exudation esoked by the growths. The frequent admixture of blood in cancerous effusions is due largely to obstruction and damage of small veins. A persistent hiemorrhagie effusion always strongly suggests malignant disease. Chylous effusions do not result from serosal carcinosis per se but from obstruction and ectass of the thorace due to its main tributions. Pecudochylous effusions are due merely to admixture of fitty degeneration products of tumours with coelomic effusions.

It is probable also that blood-borne metastatic growths in the dura mater or cranial bones may sometimes be the source of meningeal dissemination

Not a few cases have been reported m which disseminated carcinomatosis of the meninges has been unaccompanied by any demonstrable metastatic growths in the brain, as in 14 cases reviewed by Hoffmann and others reviewed by me (1934). Several reporters of such cases, notably Knierim, and Alpers and Smith, have attributed the meningeal infestation to invasion of the spinal theca from without via nerve sheaths and the spinal nerve roots. While this sequence must be admitted as quite possible, it is also possible in such cases that small undiscovered blood borne metastases in the brain, choroid plexus or meninges themselves may have been the source of the meningeal dissemination.

(2) Tumour cells in eerebrospinal fluid

As far as I know, glioma cells have not been identified in cerebrospinal fluid during life. The most likely to be found would be those of medulloblastomas, but these cells might be difficult to distinguish from lymphocytes. Tumour cells which have been identified in the fluid include those of many kinds of carcinoma (references, Willis 1934, and Duncan's case), a thymic tumour in a child (Danisch and Nedelmann), a round cell ocular sarcoma (Panton), and probably a pituitary adenoma (Cairns and Russell). Mitotic figures in tumour cells in cerebrospinal fluid were seen by Panton. Humbert and Alexieff

(3) The sites and appearances of fluid borne metastases

(a) In the leptomeninges

As might be expected, meningeal implants are usually most abundant in the basal and spinal regions, and in the latter the heavest deposits are often around the cauda equina. The posterior surface of the cord is more affected than the anterior. The spinal or cranial nerve roots may show prominent deposits. The deposits may appear as small scattered nodules or plaques, and may be mistaken for tubercles, as in my case referred to above. More often they are rather diffuse, varying in naked eye appearance from slight indefinite thickenings of the pia arachnoid only to be identified microscopically, to a massive white sheath completely enveloping the cord or brain surfaces, and sometimes filling the thecal space. These massive diffuse investments are most common with medulloblastoma. Their misdiagnosis as 'sarcomatosis' of the meninges is discussed in my earlier work.

(b) Ventricular implants

Ventricular implants usually in the form of discrete scattered nodular growths, have been seen from oligodendroghoma (Martin) papillary growths of the choroid plexus (van Wagenen, Cairns and Russell) metastatic earcinoma (Barnes) and pineal teratoma (my Case No II Chapter 61)

METASTASIS BY IMPLANTATION ON EPITHELIAL SURFACES

Medical records contain many supposed instances of metastasis by transplantation of detached tumour cells on epithelial surfaces. But there are strong grounds for rejecting this interpretation in most cases. Not only does successful

that they may have arisen from (ctopic epithelium is unnecessar). The "localized pleural mesothelioma reported by Stout and Murray (1942) is unacceptable on two grounds, the large tumour involved the left main bronchus and had a structure quite compatible with bronchual carcinoma and the uterus also con tained a milignant growth of which the lung tumour may possibly have been a metastasis. The tumour reported by Dick as an 'endothelioma of the peri cardium involved the root of the lung, and the figures show adenocrizinoma

The only tumour which I myself have ever ventured to suggest might be a primary one of a serous membrane was in a case reported in 1938. This was a polypoid growth inside a large surgically removed hydrocele sac subsequent necropsy showed this to have been a metastrisis from a small unsuspected bronchial carrenoma.

METASTASIS IN CEREBROSPINAL CAVITIES

Any malignant tumour, primary or secondary in the brain or meninges encroaching, on any surface bathed by cerebrospinal fluid may liberate tumour cells or fragments into the fluid and these may implant themselves to produce metastases on near or distant surfaces of the meninges or ventricles. Such cerebrospinal metastasis is closely similar to transcoolomic metastasis in a serious cavity con taming an effusion. (For detailed discussion see Willis 1934)

(1) The entry of tumour cells into cerebrospinal fluid

The dissemination of gliomas by way of the cerebrospinal fluid was discussed particularly by Cairns and Russell. Of the gliomas the most prone to disseminate is medulfoblastoma the usual situation of which in the roof of the fourth ventricle gives it immediate access to the eisterna magna via the formina of I usefula and Magendie. So also papillary growths of the choroid pletus frequently produce metastrises in the basal and spinal meninges. Several instances of cerebro spinal metastasis from ependymal gliomas of the fourth ventricle have been reported. Cerebral glionitis which have produced meningeal metastasise usually show gross invasion of the ventricular system or of the surface of the hrain as in the case of astrocytoma of the thilamus described by Russell and Chiris. Retino blastomis invading the optic nerves and brain may metastasize by the cerebrospinal fliuid. In a case of pinical territomic which partly filled the third ventricle (Case No. 11 Chapter 61). I saw a discrete implant in the lateral ventricle and Berblinger (1925) described a pinical tumour which had invaded the guadrageminal bodies and cerebellum and had metastasized to the meninges of the cauda equinal

When metastrice growths in the central nervous system disseminate in the meninger by way of the cerebrospinal fluid the site of invasion of the cerebrospinal fluid the site of invasion of the cerebrospinal fluid the site of invasion of the cerebro and Alexieff Willis 1934). The sequence of events is particularly clear in those cases in which metastrice growths involving the ventricular walls or in the choroid plerus are accompanied by widespread deposits in the cranial and spinal leptomeninges as in those described by Weller Ginsberg Putschar Fined Danisch and Nedelmann, and in a case of my own (1934). That the extension of metastrice growths to the paid surfaces of the brain may also initiate cerebro spinal dissemination is shown by other reported cases e.g. that of Duncan

However, there have been at least three recorded cases in which intrabronchial metastasis appears clearly to have occurred. In Hitz and Oesterlins case, a large papillary growth in the largix of a child was accompanied by multiple intrabronchial deposits in the lungs. In the case described by Vorzimer and Perla, a large mavillary adamantinoma had invaded the nasal cavity and nasopharynx and had been operated on several times under general anaesthesia necropsy revealed a large tumour cast growing in and distending the broaden of the lower lobe of the right lung, and there were no other metastases. In von Zalkas case a squamous cell carcinoma of the larynx was accompaned by a metastatic nodule in the mucosa of the right main bronchus and by multiple small intrabronchial growths in the lungs, no lymph nodal deposits were found but there were some small metastases in the kidneys. Although von Zalka admitted the objections he beheved, with good reason, I think, that aerial metastasis best explained the findings.

Since aerial metastasis can sometimes take place from the upper to the lower parts of the respiratory tract we must admit the possibility that tumours in the lungs may sometimes disseminate within the lungs themselves by the aerial route Proof of this would be well nigh impossible to obtain in human beings but animal experiments might be designed to demonstrate the inoculability of the lungs to tumours by way of the air passages. Indeed, Furth (1946) has earned out some experiments of this kind, which show that it is possible to produce tumours in the lungs of mice by the intranasal insufflation of leukaemic or carcinomatous cells.

(4) Implant metastasis in the female genital tract

In this territory local metastasis by lymphatic and venous channels is so frequent, that proof of the occurrence of surface implantation is difficult to attain There is no doubt, however, that implantation of tumours does take place in the tubal mucosa and in the endometrium. More or less convincing instances of the intra tubal implantation of fragments of abdominal or uterine carcinomas include those of Glendining Kaufmann Kundrat, Werner Offutt and Sampson (1924 and 1938). In particular, Sampson's 1938 paper fully demonstrates the occurrence of intra tubal metastases from ovarian carcinomas. Although complete proof is lacking. I think also that the work of Taussig Burckhard Novak and Offut leaves little room for doubt that ovarian or Fallopian tumours can produce endometrial implants.

On the other hand supposed instances of implant metastases of uterine tumours in the vagina or vulva are unconvincing Undoubtedly, as Kaufmann Milner and others have shown these are all attributable to submucous extensions or

local metastases by way of lymphatics or veins

(5) Implant metastasis in the urinary tract

Papillary growths of the renal pelvis or ureter, accompanied by smaller secondary growths in the lower part of the ureter or bladder are well known. Are these secondary 'growths due to surface implantation, to intra mural lymphatic extensions or to multicentric primary origin? In most cases they are certainly not due to lymphatic extension for such multiplicity is seen with

transplantation on such surfaces as the skin or the alimentary mucosa appear most improbable on general grounds but many supposed instances of metastasis by transplantation are clearly susceptible of other and preferable explanations either as multiple primary growths or metastases by other well known routes (For critical discussions, see the papers of Selimmelbusch, Bucher, Kaufmann, Milner, Bormann and Chapter VI of my 1934 work)

(1) Contact cancers of skin and other squamous stratified epithelia

Contret exteniomas of opposed epithelial surfaces are not uncommon in the skin, vulva lips tongue and check, larynx and conjunctiva. There is little doubt that multiple tumour formation in areas of similarly prepared epithelium accounts for most of these. In all of these regions we encounter multiple growths not in contact but clerify the result of multifocal neoplasia in a susceptible epithelial field as described in Chapter 7. The susceptibility of the field may consist of some well recognized pre-cancerous state such as leucoplakia in the vulva, or syphilitie disease in the oral eavity. The precise opposition of a contact cancer developing in such circumstances may well be determined by the mechanical and chemical irritation inflicted by the initial growth on the opposed already pre cancerous surface. Infrequently contact cancers may be due to direct subepithelial extensions of the initial growth. Pare instances of supposed fumour inoculation of parts of the skin remote from the initial growth may be dismissed as pure conneciences. So also may alleged cases of surface transfer of tumour from one person to another.

(2) Implant metastasis in the alimentary tract

The inherent improbability of tissue grafts taking successfully on intact surfaces bathed by digestive juices and mucus and rich in bacteria, justifies the greatest stringency in judging alleged instances of tumour implantation in the alimentary canal. Critical examination of such cases shows that the supposed implants are to be attributed either to multiple primary tumour formation of to transcoclomic or vascular metastass. Supposed implants in the oesophagus or stomach are usually due to outeropping from submucosal lymphatic extensions of the initial growth (Zahn. Bucher. Milner. Borrmann) but multicentric origin is sometimes responsible. Multiple caracinomias of the large intestine are now so well known, that I doubt whether anyone would seriously advance the implantation hypothesis to explain them. Teacher (1930) was I think the last to support this hypothesis for alimentary tumours. In a case of carcinomia of the gall bladder he attributed the multiple growths which were present in the mucosa of the small intestine to implantation of particles of growth which he supposed had passed down the hile duct into the bowel.

(3) Implant metastasis in the respiratory tract

In the great majority of cases in which secondary growths in the lungs from tumours in the upper respiratory tract have been attributed to intrabronchial metastasis this suggestion can readily be dismissed the lung metastases arrived by the usual vascular routes

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tumours of relatively benign type with no evidence of invasive spread and even in frankly malignant cases the small 'secondary' growths are often restricted to the mucosal surface and there is no sign of any cancerous lymphatics in the tissues beneath them. Multiple tumour formation in the urinary epithelium undoubtedly occurs very frequently (see Chapter 28) Is it possible then that all supposed implant tumours are multiple formations in a field of epithelium everywhere exposed to the same carcinogenic stimuli? There are three objections to this view (a) in many cases in which implantation is suggested there may be long reaches of apparently normal mucosa between the primary and 'secondary growths, with no evidence of any general inflammation or hyperplasia such as are seen in cases of aniline cancer or bilharzial cancer (b) ' implant 'tumours usually arise not fortutously in any other parts of the urinary epithelium, but at points caudal to the main tumour in the corresponding wreter or in the bladder and (c) at least one carefully studied case is recorded in which it seems clear that an extra urinary growth an adenocarcinoma of the rectum, had invaded the ureter and had produced implant metastases in the calices of the hydronephrotic kidney (Boger) If an extrinsic tumour can implant itself in the utinary passages the same capacity to a higher degree must be admitted for indigenous tumours From the available evidence then we must concede that metastasis by implanta tion may occur in the urinary passages but it will often be difficult or impossible to distinguish between this and multiple formation. Experiments might be performed to ascertain the inoculability of the urinary surfaces to tumours in anımale

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sometimes quoted serrously and approvingly. Whatever may have been the influence of Cohnheim's and Ribbert's speculations in the evolution of our knowledge of the nature and origin of tumours, it is time that modern pathologists should cease to regard them as of more than historical interest.

THE CHRONIC IRRITATION HYPOTHESIS

The view sponsored by Virchow and many others, that tumours resulted from the persistent stimulation of tissues by irritants, had much to commend it. It focused attention on extrinsic factors capible of affecting normal cells and so played an important part in advincing knowledge of occupational and experimental carcinogenesis. If in place of the term 'chronic irritation' we substitute 'carcinogenesis timult then the statements of this hypothesis by its earlier promulgators become modern. The hypothesis erred in emphasizing non specific irritation instead of specifically carcinogenic stimulation, and in implying that tumours resulted from the over stimulation of the cells by the irritants. The tissues were pictured as being "provoked" or goaded" into anarchic growth Study of pure chemical carcinogens has dispelled this misconception, these substances are not irritating in the ordinary sense. Nevertheless, as described in Chapter 4, non specific injuries or irritations may ret as co carcinogens in augmenting or accelerating tumour formation in tissues already prepared by the action of carcinogenic agents.

Several elaborations of the irritation hypothesis require comment. The most important of these is connected with the part played by trauma in the genesis of tumours. There is searcely any kind of tumour for which trauma has not been blamed in some or many cases, this applies not only to tumours of external and easily injured parts such as the integuments breast, testis and bones but to those of deeply seated protected parts such as the brain, bronch and other viscera. The possible part played by trauma in the causation of particular tumours will be discussed in the chapters of Part II, here it must suffice to make the general statement that simple injury of healthy tissues is rarely, if ever a sufficient cause of neoplasia but, as already stated injury can precipitate neoplasia in carcinogenically prepared tissues.

Another special extension of the irritation hypothesis is Handley's view 'that the origin of cancer is intimately associated with local obstruction of the lymph vessels' that lymph stasis lies at the root of cancer' Admirable though much of Handley's work has been, most pathologists will agree that he has been unduly preoccupied with the lymphatic system both as regards metastasis and causation

Several workers have postulated a relationship between tuberculosis and cancer. Of these the most insistent was Cherry who in a score of papers tried to show statistically that these two diseases were causally related "that a partner ship exists between them", "that the two may be regarded as related forms of one disease and 'that the mastery of the one should soon lead to the control of the other." Cherry's arguments based mainly on mortality statistics, are nullified by the great degree of diagnostic error hidden in these (see Chapter 5). It is pertinent to add also that anyone experienced in necropsy work, will know how frequently tuberculous lessons quiescent or active are to be found in adults.

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Principles of Medical Statistics", 1939, p 133) CHill

The misconcention that cancer is peculiarly a disease of civilization is now little more than a popular fallacy Its latest expression was Cope s book, the title of which- Cancer Chilization Degeneration' -- sufficiently indicates its tenor But this view has not been without some better-informed subscribers notably Gilford, who cited Cope approvingly and who also saw in 'national degeneracy ', in the bad habits and bad heredity of civilized life and in premature senescence of tissues, the basic causes of cancer' Gilford's book is a useful compilation of references and facts about tumours, built, however, around this central preconception (It is surely significant that Gilford was the describer of the condition of premature sensity progeria)

With regard to opinions such as the foregoing, the following facts discussed in earlier chapters may be recalled that cancer is not peculiar to civilized peoples but occurs in all races of man and all classes of animals, that its incidence in different human communities depends on their respective age compositions, though its site incidence varies with local habits and exposure to special factors, and that increasing age brings more cancer, not because of senility of tissues, but because of the longer opportunity for the continued action of carcinogenic stimuli and for expiry of the long latent periods which intervene between the application of such stimuli and the appearance of the resulting tumours That civilization causes cancer is of course, true in the sense that many of the tumours of civilized man are evoked by identifiable carcinogens in his environment, such as tar, oils, arsenic or radium and in the sense that carcinomas of the alimentary canal may well be due largely to avoidable dietetic habits or carcinomas of the breast to 'unnatural' reproductive and lactational habits Effective prophylaxis by identification and avoidance of these carcinogenic factors is the main aim of experimental cancer research, and the great successes achieved in this field during the last three decades give the he to Gilford's denunciation that 'nothing of any value has emerged from it '.

CANCER DIATHESIS

Probably the last serious attempt to uphold the old humoral hypothesis, that malignant tumours and their metastases were all manifestations of a constitutional cancerous dyscrasia was at the meeting of the Pathological Society of London in 1874 It would be unnecessary to refer to the long obsolete notion of dyscrasia, did it not still appear occasionally in modern pseudo scientific form. Thus, as recently, as 1934, a well known and experienced pathologist Fischer Wasels published a booklet contending that cancer can develop only in patients with a dietary alkalosis and recommending an elaborate dietetic and hygienic regimen for cancer sufferers This included restriction of sugar salt cholesterol and vitamin B, administration of calcium vitamin D, and splenic extracts, local and will therefore realize the futility of attempting to correlate the incidence of cancer and previous tuberculous infection

PARASITIC HYPOTHESES

Parasitic hypotheses differ fundamentally from irritational hypotheses the latter pictured the irritation as bringing about irrevocable neoplastic cellular changes which then persisted independently of any further irritation the former suppose the responsible parasite to multiply in, and maintain the vicious growth of, the tumour Although tumours can be evoked by the presence of metazoal parasites, such as biharzia or cystiecreus these tumours are not relevant in the present connexion since they and their metastases do not depend for their con tinued growth on the presence of the parasites. Bacteria, spirochaetes protozoa fungi and viruses have all in turn been blamed as the indwelling causes of tumour growth. Only the last of these remain for serious discussion.

Rous and his collaborators in America, Gye and Purdy in England and Blumenthal and eo workers in Germany, have been the chief upholders of the view that mammalian tumours may like the filterable tumours of birds be due to a virus which multiplies in and maintains the pathological growth of the colls. This question was discussed in Chapter 4 where it was pointed out that the filterable tumours of birds the Shope tumour of rabbits and Lucke's frog tumours are all deededly peculiar diseases, and not necessarily valid exemplars of tumours in general. At all events many attempts by experienced workers to demonstrate the presence of a filterable agent in malignant mammalian tumours have failed and the supposed successes of Blumenthal and others have been shown to be fallacious (see the experiments of Flaks and Wagner, cited in Chapter 6). The view, gaining increasing support, that the so called tumour viruses' may not be parasitic miero organisms at all but abnormal proteins of the cells themselves, is discussed below under 'Cyntologame hypotheses'.

Webster depicted structures which he interpreted as virus inclusion bodies in enneer cells, he also believed that he could discern periodic fluctuations in the growth of tumours which he thought explicable only on the theory that they are essentially the outward representation of changes in the life-cycle of the erusative agent However Webster's inclusion bodies 'are well known to every histopathologist they are the same kinds of structures as the Russell s bodies and Plimmer's bodies', which long ago were thought to be cancer parasites of another kind-blastomycetes-but which we now know to be only abnormal cell products. The cells of malignant tumours especially rapidly growing ones display a great variety of abnormal nuclear and extonlasmic struc tures, some of which simulate closely the appearance of the inclusion bodies of virus diseases. Virus workers must avoid being misled by these appearances With Webster's observations regarding periodicity in the recurrence and growth of tumours neither my own experience, nor that of other pathologists and clinicians with whom I have discussed the question is in accord and as far as I know no endorsements of them by other workers have been published

HYPOTHLSES BLAMING CIVILIZATION

"It has been observed that while the death rate from cancer has been rising the sale of bananas in England and Wales has also been increasing. No one (so

of the cells any intra-cellular parasite, any senescence or any genetic changes in the cells, but may consist in irreversible metabolic and cytoplasmic alterations occasioned by the application of carcinogenic agents, alterations which may well be conceived to differ in degree from tumour to tumour

Penfold (1922) likened tumour formation to the development of secondary papillae in bacterial colonies. These result from the selective action of poisons or particular nutritive substances favouring the growth of variants in the colony Penfold suggested that a carcinogenic agent might play a similar part in selecting particular cell variants in the tissues.

Warburg (1925) attempted to explain tumour genesis as the result of oxygen deciency in tissues causing selective survival of cells of high glycolytuc powers a hypothesis which subsequent work has shown to be untenable (see Chapter 8)

From his work on the effects of carcinogens on protozoa, Mottram (1942) was of the opinion that neoplastic change may well be cytoplasmic rather than nuclear. He rightly pointed out that the cytoplasm contains many important parts such as Golgi apparatus, mucchondria and chromidia, one of which might well be the important point of action of carcinogenic agents.

Haddow's work on the growth inhibitory action of carcinogenic substances led him to some important reflections on the genesis of tumours (1938 and 1944) Briefly his argument was as follows carcinogenic agents inhibit the growth and metabolism of cells to which they are applied, the cells react to this by an alteration of their metabolism, which has "survival value and in effect confers a biological advantage", there thus appears "a new cell type with an increased rate of growth and, probably with other physiological properties which enable it to resist, or to escape from, the increasing restraint brought about by environmental changes. Haddow saw in this change a close parallel with the formation of vigorously growing secondary colonies in old bacterial cultures, as suggested earlier by Penfold. It is important to emphasize that the alteration does not consist in the acquisition of a new function so much as in variation in the property of growth which is normally possessed by the majority of cells."

With regard to the irreversibility of the change once established Haddow (1944) drew attention to recent work on plasmagenes and cytoplasmic inheritance and to the view that cellular differentiation is determined by hypothetical particles in the cytoplasm. The production of different characters in cells with the same nuclear genes would thus be brought about by differential segregation of these cytoplasmic determiners at cell division Now the degree of differentia tion is an important individual character of tumours (see Chapter 8) of a given cell type can be placed in a continuous series ranging from a near perfect reproduction of the histology of the parent tissue to a condition in which no specific differentiation can be recognized whatever The extent of such The chemical carcinogen departure is relatively stable for any given tumour" produces a change in the habit of growth of the cell but as the change is quite permanent it persists indefinitely after the initial cause has disappeared the mechanism which permits unlimited growth must clearly reside in the cell is obviously a possi itself That it may reside partly at least in the cytoplasm bility for future investigation

The possible nature of the agents of the filterable tumours is relevant here Many of the plant viruses appear to be autocatalytic proteins of host cell origin



the tumour we as yet know next to nothing. The nature of this response is, however, no less understood than the nature of inflammatory response to a bacterial parasite. When we say that the tubercle bacilius is the cause of tuberculosis'. we state only part of the truth, and that the smaller part. The tubercle baculus does not cause tuberculosis in a test tube, or in some species of animals, or even in some human beings "Tuberculosis" involves two reagents, the bacillus and the susceptible tissue into which it is introduced. The intrinsic properties of the tissues which render them susceptible and determine their tuberculous reaction are as yet unknown. In this sense, then, the tuberculous reaction is no less mysterious than the neoplastic reaction, yet we do not attempt to explain the former by imagining a gene mutation or a "virus" in the altered cells. When we can say of a particular tumour "That tumour resulted from the application of benzpyrene, or ultra violet rays or X-rays", then we know every bit as much about its cause as we know about the cause of tuberculosis or of any other inflammatory disease. What makes the neoplastic reaction seem more mysterious to us than the inflammatory reaction is its irreversible character, and its long delayed onset perhaps long after the agent which evoked it has ceased to act. At present we have achieved only vague glimpses of the possible nature of the cellular changes involved, but increasing knowledge of the mechanisms of cell growth and differentiation will undoubtedly clarify our view

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best presentation of proper views on causation)

a view expressed also by Stanley regarding the Shope papilloma virus (Chapter 6) Perhaps then, filterable tumour agents and plasmagenes are related substances At all events, the view that the former are parasitie micro organisms has steadily lost support. In 1925 Nicholson suggested that Rous sarcoma virus "might be not a virus, but 'a chemical substance produced by cellular action." In 1933 Boycott said 'if one postulates a normal virus occurring in normal cells, one had better call it something other than a virus. In 1942 Needham wrote, 'Why should we not call the primary evocator a virus, since it makes more of itself parallel with the histological change which it produces? The objection to the virus theory of cancer lies in the fact that it emphasizes primarily the exogenous origin of uncontrolled specific proliferation. But on grounds of methodological simplicity ought we not to prefer the metabolism existing also in all the cells of the organism?

Needham discusses in detail the chemical relationships of the carcinogenic hydrocarbons the sex hormones and the group of sterols to which the embryonic evocating substances belong he suggeds that embryonic evocation sex hormone action and carcinogenesis may well be related phenomena, and insists that one of the most important aspects of cancerous growth is its escape from the

controlling pattern or individuation field of the tissues '

Modern biology is then, turning to the simplest theory of all regarding the nature of neoplastic change—the theory namely that the normal cells of the body are variable structures reacting in diverse ways to changes in their environment by changing their own habits of growth and metabolism, and that tumour cells are but variants of normal cells produced in response to external careinogenic agents. Nicholson's prescient insistence on this principle is summarized in the following citations from his Study No XIII (1933). 'I see in timour formation the shifting more or less of the somatic ratio in the direction of accelerated growth with consequent—necessary—retarding of physiological action (and its morphological expression histological differentiation). The secret of tumour formation lies for me in the mechanism that determines the new ratio.

explain tumour formation with a misconception like autonomy or uncon trolled growth or with a hypothesis like a virus chromosomatic malformation or mutation et hoc genus omne is idly to scratch the surface. for the problem is rooted in the very being and coming to be of organismic evolution and individu ation, development and existence form and function Our knowledge of tumour formation is a pretty accurate measure of our understanding of growth and development. Advance in either means advance in both to ask crucial questions of biology, and are beginning to get answers. We are beginning to do without unphysiological, unbiological and essentially unnatural and incomprehensible morbid reactions of the organism and to see that everything is physiological except the purely adventitious extrinsic stimulus. We are beginning to see that tumour formation is reaction to excitation growth and differentiation of cells capable of these functions, consequent acquisition of characters maintenance and transmission to future cell generations of the characters thus acquired-in sum the first principles of individuation and life

Briefly tumour formation is the final product of the cumulative response of cells to certain environmental stimuli. Of recent years we have learnt a great deal about some of these stimuli. of the all important cellular response which yields

CHAPTER 12

RECAPITED ATION

DEFINITION

OUR DETINITION of a tumour, as an abnarmal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change, can now in the light of Chripters 4, 8 and 11, be much better appreciated Nichol son's failure of co-ordination", or Needham's "escape from the controlling pattern or individuation field", is the essential quality in a neoplasm. This escape is bound up with an irreversible change in the metabolism and multiplication of the cells—a change which is transmitted indefinitely to their descendants and which persists independently of the carcinogenic stimuli which initiated it. This permanent and transmissible habit of excessive uncoordinated growth distinguishes tumours from all other puthological overgrowths, whether hyperplasms reparative proliferations or malformations.

CLASSIFICATION AND NOMENCLATURE

The only fundamental basis of tumour classification is histogenesis i c according to the type cells from which tumours spring and of which they consist. All other features, such as rate of growth, degree of differentiation, and, with these, degree of innocence or maligniney are subsidiary. The pirenehyma of most tumours consists of cells of a single type, so that their histogenetic classification and nomenclature run parallel with the histological grouping of normal tissues. Some tumours however, are composite containing two or more neoplastic tissues many of these, namely, the mixed tumours of infancy and the territomis, arise during early development from still immature tissues. Apart from the important distinction between the relatively rare truly embryonic tumours, which arise from and continue to consist of embryonic tissues on the one hand, and the common tumours of adult tissues on the other hand, the embryonic origin of tissues are of no interest in tumour classification. Tumours are anomales of growth and differentiation of particular kinds of tissues, the original germ layer derivations of these are irrelevant. Causition also is irrelevant in classification different carcinogens applied to a given tissue evoke similar tumours while a single carcinogen applied to different tissues may evoke a variety of tumours.

INNOCENCE AND MALIGNANCY

^{&#}x27;Innocent and 'malignant" are relative terms, of value in the art of prognosis but not denoting distinct species of tumours. The individual tumours of a particular cell type usually show a complete range of structure and behaviour, from those which grow slowly, attain high differentiation and remain non invasive and local to those which grow rapidly, differentiate poorly invade and

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and fallacies of statistics in general, but also with the medical aspects of his problem, including the bases and reliability of diagnosis, the use of pathological nomenclature, the efficacy of treatments, the methods of recording, etc. Unless he has this dual knowledge, he is unlikely to escape falling into some unsuspected trap, and, if he has it he will realize how limited the applicability of the statistical approach to many of the problems connected with tumours

Purely statistical errors are often committed by writers of papers on tumours But more important even than these, are the frequent errors of tumour diagnosiserrors which of course if present in any considerable proportions, necessarily vitiate any statistical analyses whatever The main theme of Chapter 5 was to show what proportions of the clinical diagnoses of the particular kinds of tumours are likely to be erroneous, and it was concluded that, except for the more accessible tumours, such as those of the skin breast buccal cavity or uterus general clinical diagnosis is fraught with such a high degree of error that many statistical studies are vilueless. Surgical or post-mortem series of cases of proven pathological nature afford valid data for statistical deductions within limits imposed by the selected nature of the material. But for many major statistical problems such selected series are of course unsuitable For these and other reasons comparisons of the mortality figures of different countries or of clinical records in different communities or clinics, and estimates of trends in tumour incidence, must be viewed with great caution

TUMOURS IN ANIMALS

Tumours resembling those of man occur in all classes of vertebrates, in both the wild and captive state—and there is no main kind of human tumour of which counterparts do not occur in one or more other species of mammal. The study of animal tumours is often helpful in clueidating the histogenesis of the corresponding human ones, and the incidence of particular tumours in mammals may well give clues regarding the responsible careinogenic factors. Transplanted tumours are of limited value in the study of many of the problems of tumour behaviour or response to therapeutic agents, for these purposes, spontaneous tumours or those evoked experimentally, by careinogens are often preferable.

THE MODE OF ORIGIN OF TUMOURS

Contrary to the still prevalent unicentric idea of tumour origin—a relic of the erroneous hypotheses of Cohnheim and Ribbert—tumours do not arise from single minute foce but from considerable fields of prepared tissue. Many small, and some large, tumours still show clear evidence that tumour genesis the transformation of the tissue of the susceptible field into tumour, was still in progress when the tumours were existed. Should existion have failed to remove the whole of the tumour formative field, recurrence of the growth may ensue, not from tumour residues as such, but from new areas of cancerous change in the residual tissue of the field. In extensive potentially cancerous fields multifocal development of cancer is often to be observed, good examples include the multiple carcinomas in polyposis of the colon or in xeroderma pigmentosum or in the

disseminate There is a broad parallelism, but with many individual exceptions between degree of malignancy and degree of analplasia, a parallelism long recognized by pathologists as of value in prognosis. Attempts to prognose by grading 't timours numerically however, though they may impress the clinician by their spurrous appearance of precision are always highly arbitrary and often fallacious. A high degree of structural organization is compatible with malignancy, and poor organization with innocence 'Malignant cachexia does not exist, the debility, maintitution and anaemia of many cases of advanced malignant disease are merely the results of interference with important bodily functions by the tumours

THE EXPERIMENTAL PRODUCTION OF TUMOURS

Recent achievements in this field of research have been epochal. Tumours of almost all kinds have been produced by pure chemical substances or by various physical agents and many of these experimentally identified carcinogens are clearly the same as those responsible for occupational and other tumours in human beings. Already the experimental work has thus shown the way to effective prophylans of certain human tumours eg mule spinner is cancer, actinic skin cancers rachum and X ray cancers, aniline worker is cancer of the bladder etc. As the experimentalist goes on as he will do to identify more and more carcinogens in our environment—in our food and drinks our occupational materials and reagents our tobacco smoke drugs and cosmetics—so an extending basis for prophylaxis will be laid. Whether and to what extent the people generally will be prepared to avoid the noxious factors detected will be the concern not of the experimentalist.

Not only has experimental work disclosed a great variety of exogenous carcinogens but it has shown also that endogenous carcinogens may be formed in the body itself as the result of disturbed hormonal states or other pathological conditions. For obvious reasons, work in this field is more difficult and complex than the search for exogenous carcinogens, but future research will identify the chemical carcinogens formed in diseased itsues and will unravel the factors involved in their production. This knowledge will probably elucidate the causation of most of the tumours of the breast uterus prostate and ductless glands and will point the way to their prevention.

In yet a third way experimental carcinogenesis is full of great promise. By studying the chemical properties of carcinogens, their structural and functional effects on tissues, their absorption metabolism and fate in the body and the phenomena of anti-carcinogenesis and co-carcinogenesis, it is not unlikely that something may be learnt of the nature of the neoplastic change in cells the ultimate secret of tumour formation.

THE STATISTICAL STUDY OF TUMOURS

Many pitfalls beset the student of tumour statistics. Before venturing on any deductions whatever—even as regards such seemingly simple questions as the age mendence of a particular kind of tumour or the relative frequencies of tumours of different kinds—he must be thoroughly acquainted, not only with the methods

important general property of tumours, their growth is susceptible to external influences. Mitotic activity varies in different parts of a tumour or in metastases in different situations some innocent, and occasional malignant, tumours spontaneously cease growing and retrogress, some malignant tumours show unaccountable temporary arrests of growth, long delayed recurrence or long delayed metastasis, the growth of some tumours, especially those of hormonally controlled tissues varies with the endocrine state of the patient or with the administration of particular hormones, cancinogenic substances inhibit tumour growth. All these facts encourage the hope that, when research has elucidated the controlling factors, an effective chemotherapy of cancer may not be impossible of achievement.

THE DIRECT SPREAD OF TUMOURS

As a tumour increases in bulk by proliferation of its cells, it finds accommodation in the tissues in one or both of two ways—by expansion or by infiltration. Invasive ness does not depend on any single property of the tumour cells, nor on any special changes in the invaded tissues, it is one attribute of the neoplastic cellular change as a whole differing from tuniour to tumour but nearly constant in each

Invasiveness confers on a tumour the power to penetrate into any or all available interstices or preformed channels in the tissues and to spread in these away from the primary site for short or long distances. The paths of invasion are intercellular and intracellular spaces, lymph vessels blood vessels coelomic and cerebrospinal spaces and epithelial cavities. Invasion of preformed paths sets the stage for metastasis by transport

METASTASIS

Metastasis means the transfer of detached tumour particles within vascular, coelomic, cerebrospinal or epithelial channels, and their successful lodgement and survival to produce discrete secondary growths at new sites. It is a form of natural grafting or transplantation of the tumour from site to site. Not all grafts are successful dissemination and lodgement of tumour particles may occur but no metastases develop, the arrested cells failing to multiply or survive in their new environment. Abortive tumor embolism is commonly demonstrable in the lungs but doubtless occurs in most other tissues also, it accounts for many of the peculiarities of distribution of metastatic growths. Elucidation of the chemical and other factors which determine the success or failure of disseminated tumour cells to survive and grow in new sites might assist in the search for effective chemotherapeutic agents. The great series of grafting experiments already performed for us in the dissemination and metastasis of tumours is thus worthy of close study, this should be supplemented by experimental investigations of metastasis like those described in Chapter 6

The study of meta-tasis is of immediate practical importance to the clinician not merely because of its obvious bearing on operability and prognosis, but also because metastatic growths may be the first or main manifestations of otherwise symptomless or unsuspected primary tumours. As was noted in Chapter 5 main misdiagnoses are due to secondary growths masquerading clinically as

The field origin of tumours is not only clear from structural studies but from experimental work. When a carcinogen is applied to a tissue it is not applied to

breast

a sincle minute focus but to a more or less extensive field of the tissue Visible tumour formation usually commences at one or more small foci in that field but the neoplastic change extends from these to other parts of the field distribution and timing of this change is determined, no doubt by the distribution and intensity of the earcinogenic stimulation to which the whole field has been subjected and to co carcinogenic injuries to which it may also have been exposed The spread of tumour genesis in the field does not imply the spread of any parasite or chemical influence from tumour cells to adjacent normal ones

THE STRUCTURE AND GROWTH OF TUMOURS

Most tumours show remarkable structural individuality and stability Throughout a long metastatic career or during a long series of transplantations a particular tumour usually maintains not only its own characteristic degree of organization and general rate of growth, but also many minor peculiarities of structure such as its range of variation metaplastic propensities cytological details and the nature and amount of stromal reactions excited by it Clearly then. whatever the fundamental nature of the neoplastic change may be it varies in degree, and perhaps in minor ways in kind also from tumour to tumour

The range of structural variation in a single tumour is often such as to preclude its allocation to any particular histological sub group within its class. Such histological names as spheroidal cell carcinoma, adenocarcinoma oat-cell carcinoma, etc. have only a descriptive value to designate the predominant structural variants in particular turiours. They do not denote distinct species. the species are corcinoma of the breast carcinoma of the bronchus etc. and histological sub division of these is always arbitrary and often quite mapplicable A single tumour may show all the varieties of structure of which its species is capable

Anaplastic tumours, especially carcinomas often display misleading micro scopical appearances simulating those of other kinds of tumours growing carcinomas have often been misdiagnosed as sarcomas carcino sarcoma has been particularly fallible the great majority of tumours so designated have been pleomorphic earcinomas, truly composite earcino sarcomas do occur but are very rare. The mammary fibro adenomas however. are truly composite growths the fibromatous component of which sometimes becomes sarcomatous

Naturally enough the cells of rapidly growing tumours often show abnormali ties of structure and metabolism but in neither their cytology nor chemistry have the cells of well differentiated tumours been shown to differ from normal cells in any significant or constant characters. That tumour cells are permanently altered cells there is no doubt, but the alteration is more subtle than our micro scopical and chemical methods have so far proved capable of detecting

While relative constancy of individual structure and habits of growth is an

CHAPTER 13

EPITHELIAL TUMOURS OF THE BREAST

HISTORICAL INTRODUCTION

For MANY reasons—notably its great frequency and lethal properties, its nearly complete restriction to the female breast, its now proven relationship to the hor monal control of the breast and to disturbed breast function, and its experimental production—mammary carcinoma has excited more interest than any other kind of tumour

Because of the external situation of the breast, carcinomas and other tumours of this organ were no doubt amongst the first tumours to be recognized and named by the ancient Greeks Hippocrates and his contemporaries knew of cancer of the breast, but, earlier still and perhaps the first specifically reported instance of breast tumour, was that recorded by Herodotus Atossa, the daughter of Cyrus and the wife of Darius I about 520 BC 'had a tumour on her breast, after some time it burst, and spread considerably. As long as it was small she concealed it, and from delicacy informed no one of it, when it became dangerous, she sent for Democedes and showed it to him" Democedes is said to have cured it, but by what means or how permanently we are not told. and of course, as with all early records, we cannot be sure of the nature of the lesion Early in the first century A D. Celsus practised amoutation of the breast for early cancers, but considered that operation on advanced cases only aggravated the disease (Castiglioni) Indicative of the persistence of the doctrine of humours is the following statement from Paul of Aegina in the 7th century "Cancer particularly frequent in the breasts of women, because owing to their laxity they readily admit the thick humours which occasion it For cancers are formed by black bile over-heated, and if particularly acrid, it is attended with ulceration

The veins are filled and stretched around like the feet of the animal called cancer (crab) and hence the disease has got its appellation. But some say that it is so called because it adheres to any part which it seizes upon in an obstinate manner like the crab." Severino's account of 'strumas of the breast' (1632) is noteworthy because for the first time it distinguished between beinging and malignant tumours of the organ and also contained passages suggesting that the author recognized what we now call cystic hyperplasia as a pre cancerous condition.

The state of knowledge of tumours of the breast—and of tumours generally—in the latter part of the eighteenth century is well shown by the following citations from John Hunter's lectures Speaking of "the scrofulous breast (meaning the fibro adenomatous), Hunter described a tumour "which came on at the age of twenty-six, and increased gradually to thirty eight. It was sixteen or eighteen pounds in weight. In this case there was no disease leading to the axilla as in cancer, so that I dissected it out and it healed kindly. It was perfectly circum scribed which is never the case with cancer, when of any size. Cancer may be

primary ones. Chincians still have far too little knowledge of this important source of diagnostic mistakes.

HYPOTHESES OF NEOPLASIA

As in so many other difficult fields of research, fantasy has often been substituted for the difficult admission — Ignoramus" But while the imaginative have been producing a crop of conflicting — theories" histopathologists and experimentalists have been building up a secure foundation of knowledge of tumour equivation and behaviour and-healthiest omen-pathologists are beginning to pay atten tion to biologists, and biologists to pathologists. All are coming slowly to realize that progress in embryology in genetics in cytology, in biochemistry, in endocrinology and in pathology are all inextricably linked, that pathology is extended physiology and that disturbances of growth studied by one specialist are of interest to all. Tumours constitute one of the major forms of growth disturbance in response to certain external acouts-carcinogenic agents-applied to cells Many of these external agents are being identified, the nature of the internal response the neoplastic change in the affected cells still needs elucidation. But, that this will come with increasing knowledge of cell chemistry of the mechanisms of cell differentiation and co ordination and of the mode of action of carcinorens. there is no doubt. The first steps in this elucidation have been taken, when it has been completed it will be found that neither embryonic cell rests nor their reverse-senescent cells, neither ultra microscopic parasites nor disordered chromosomes nor mutant genes are concerned in the change from normal to neoplastic cells

discharge?

contamination" Of incurable cases, "When the glands become indurated the fluids are not absorbed, in consequence of which there is a stagnation and extra vasition of serum causing oedema of the parts around. The arm and the integuments of the chest below, swell, and the fingers are sometimes rendered immovable, and very painful. In this stage sympathetic cancerous tumours often arise at a distance, and heetic fever comes on." Hunter rejected the view that cancer produced a specific kind of cachexia. "this is no more than the effect of all long continued irritations, or sores which are not disposed to heal, but no peculiar effect is produced from this affection on the constitution Cancer appears to give rise to no constitutional symptoms, except such as would

In its main essentials then Hunter's knowledge of mammary cancer was surprisingly complete—about as complete indeed as it could be, prior to the advent of histopathological methods and the more precise means these afforded for the specific identification of tumours. Cheatle and Cutler's admirable monograph is the culmination of the histological study of mammary tumours.

irise in other diseases from the long continued wearing pain and perpetual

TYPES OF MAMMARY TUMOURS

Epithelial tumours of the breast comprise

- (1) Fibro adenoma and adenoma
- (2) Duct papilloma and papillary cystadenoma
- (3) Carcinoma
- (4) Paget's disease of the nipple

While the first of these is a distinct sub group, the other three are closely related to one another. No sharp distinction can be drawn between being papillomas and papillary crienomas of the ducts, papillomas may coexist with invasive carcinoma, crienoma of the manmary epithelium almost always coexists with Paget's disease, and all three forms of growth may occur in the one breast.

The relative frequency with which the four types of tumour are encountered in surgical practice is indicated roughly by the following figures, showing the numbers of the microscopical identifications of all surgically removed mammary tumours made at the Alfred Hospital, McDourne over a period of 14 years

| Carcinomas of female breas | st ~ | ~ | | _ | _ | 550 cases |
|----------------------------|------|---|---|---|---|-----------|
| Carcinomas of male breast | - | _ | - | _ | _ | 2, |
| Fibro adenomas | | _ | _ | _ | _ | 130 , |
| Benign papillomas - | - | _ | _ | _ | _ | 15 ,, |
| Paget s disease | _ | _ | - | - | - | 6, |
| Sarcoma | - | - | _ | _ | _ | 1 case |

The number of papillomas is probably underestimated, it includes only simple localized growths unaecompanied by earcinoma, and excludes some papillomas present in cancerous breasts. Paget's disease was accompanied by intra-mammary carcinoma in all 6 cases. According to these figures the surgeon might expect to see mammary earcinoma about 4 times as frequently as

so at first, when small and loose in the cellular membrane, but when as large as a large egg it affects the surrounding parts and is more diffused. True scrofula, however if attended with inflammation will also adhere and diffuse and lose itself in the surrounding parts, so as to put on a cancerous appearance. He described how, in well established cancer, the skin will be less movable, the imple more or less retracted and the lymphatic glands going to the axilla will swell. In cancer the surrounding parts that are affected by continued sympathy also become cancerous near the skin that is all the parts become blended in one mass. When scirribus is entirely let alone it is commonly very slow. A small lump in the breast may sometimes continue for many years, but whenever inflammation takes place its progress is accelerated. Sometimes the first symptom of a cancer in the breast is a bleeding from the nipple

That Hunter recognized the surgical importance of the multicentric origin of some mammary cancers and their association with cystic changes in the breast is shown by the following passage it (cancer) often arises in distinct points of the same breast but seldom at the same period and some of these may be so much in their infancy when the operation is performed as not to be observable, but afterwards increase and require a second operation. The surrounding substance of the breast has often little tumours, sometimes containing a blackish fluid these may be called cancerous hydatids. It is therefore best to extirpate the breast completely at once to remove the whole complaint

Hunter's views on operability also were remarkably sound Now to know if a cancer is proper for operation two things should be considered viz the cancer itself and its consequences. Great attention should be paid to the tumour. whether it is movable or not for as the disease is further extended so the parts are more united to the tumour If the tumour is not only movable but the part naturally so then there is no impropriety in removing it with regard to the tumour itself but before removing it we must consider if there are any conse We should examine for example the glands in the groin or axilla to ascertain if they are thickened or swoln All the above circumstances being considered and no objections existing the breast may be safely removed if any consequent cancers easy of extirpation are found, they may be safely removed also But it requires very great caution to know if any of these consequent tumours are within proper reach for we are apt to be deceived in regard to the lymphatic glands which often appear movable when on extirpation a chain of them is found to run far beyond out of our reach, which renders the operation unsue cessful As this is not easily known I would in most cases, where the lymphatic glands are considerably enlarged, advise that the case should be let alone' Surely advice as sound to day as then !

Regarding post operative recurrence Hunter observed This is either in the cicatrix or in the lymphatic glands I have sometimes seen after the operation the glands under the clavicle will and push out the clavicle The contamination extends in other instances on the inside of the sternum in the course of the internal mammary artery sometimes these consequent cancers appear long after the operation even years. In an earlier lecture he had stated I have seen instances where it was years after all continuance of the cruse was removed before the glands in the armpth had taken on diseased action after

(a) Age and sex incidence

Fibro adenomas are rare before puberty, but are the commonest mammary tumours between then and the twenty-fifth or thirtieth year. Most of them are discovered during this period, but some, especially those with predominant intra-canalicular structure, do not appear until later. The large intra canalicular tumours are seen usually in middle aged or elderly people, though there has often been a long history of an enlarging lump.

Fibro adenomas are very rare in the male breast, Chentle and Cutler cite recorded cases, Searff and Smith record 4 examples in a series of 65 mammary lessons in males

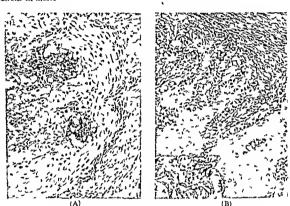


Fig. 53 — Fibro adenoma of dog $A = \text{calcifying cartilage } B \approx \text{bone } (\times 120)$

(b) Fibro adenomas in animals

These growths have rarely been observed in any species of mammals other than dogs and rats in both of which however they occur frequently

(i) Dogs—Mammary fibro adenomas are common in bitches of most breeds (Feldman, Schlotthauer, and see the table in Chapter 6) They are usually found in middle aged or old animals but are often known to have been present for some years or are large tumours clearly of long duration when first noticed They are often multiple in one breast or in several breasts are often associated with cystic hyperplastic changes and sometimes carcinomatous changes supervene in them. In the 17 dogs with fibro adenomas studied by Rudduck and me the animals ranged in age from 6 to 12 years, the tumours ranged from 1 to 11 centimetres in diameter, were multiple in 5 cases, and showed supervening care noma in 2 cases. The microscopical appearances of cartilage may be simulated

fibro adenoma and about 40 times as frequently as simple papilloma while Paget's disease may accompany mammary caremoma in about 1 per cent of cases

FIBRO-ADENOVA AND ADENOVA

I apply these names in the usually accepted sense distinguishing fibro adenoma sharply from duct papilloma. Because of the papillary pattern of the intra-carnheular type of fibro adenoma some writers (e.g. Saphir and Parker) have



Fig. 51 —Fibro adenoma of dog showing intra-canalicular structure. The tumour measured 11 centimetres in diameter. (x 80)

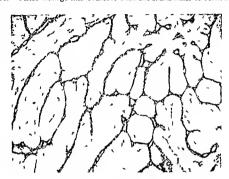


Fig. 52 — Fibro-adenoma of dog showing glandular tissue and cartilage in close juxtaposition (\times 129)

called this growth fibro papilloma but I think it better not to confuse the fibro adenomas and duct papillomas even in name for the two have little in common

(c) Mode of origin

By examination of the breast tissue around fibro adenomas, Nicholson's and Cheatle and Cutler's observations on their mode of origin is readily confirmed. The surrounding tissue almost always shows some degree of lobular hyperplasia of adolescent type ("mazoplasia" of Cheatle, "adenosis" of Dawson) with the development of multiple small satellite fibro adenomas or incipient fibro adenomatous foci. These enlarge and coalesce with the main mass to form a lobulated



Fio 55 -- Intra-canalicular fibro adenoma (× 50)

tumour, the early growth of which is therefore by accretion as well as by proliferation. Transitions from breast to tumour tissue are often to be seen and the tumours, though seeming to be well circumscribed and easily shelled out are not strictly encapsulated. The bed of tissue around a fibro adenoma is thus a field of potential similar change, and following simple enucleation of the growth recurrence may ensue from new foci of growth developing in this tissue. The proper surgical treatment is therefore excision of the segment of breast containing the tumour. Multiple fibro adenomas are not uncommon, they are usually in close proximity to one another, but are sometimes remote or bilateral

(d) Structure

Two kinds of pattern are recognized in fibro adenomas (i) peri canalicular or peri acinar, and (ii) intra canalicular, the former predominating in the tumours of youth the latter in those which appear after the age of 30 There are not two distinct types of tumour, however many fibro adenomas show both kinds of structure

(i) Peri canalicular structure—Thus shows sim normal appearance set in a variable, usually exces peri ductal connective tissue as in Fig 54. This plump fusiform fibroblests and wavy delicate non co ry ducts of ne of characte ured tissue he proport by epathelial cells scattered in mucinous secretion as in the pleomorphic tumours of salivary glands, but true cartilage or bone often develops by metaplasia in the fibromatous tissue of the tumours. Cartilage or bone was present in 6 of our 17 cases, and in one case haemopoietic marrow had developed in a mass of bone. Apart from the frequent presence of these metaplastic tissues, the cannet tumours are in most respects similar in structure to the human ones. (See Figs 51-53).

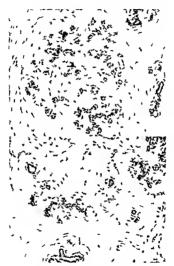


Fig. 54 -- Fibro adenoma of rat (× 120)

(ii) Rats — Fibro adenomas are the most frequent mammary tumours in rats (Curtis et al., Ratclift. Wright et al. and see Fig. 54). Different tumours contain the glandular and fibromatous components in all possible relative proportions from nearly pure adenoma to pure fibroma. The tumours are transplant able and by successive transplantation the epithelial component suffers elimination from some tumours leaving pure fibroma and in some instances this becomes sorcomatous (Robinson and Grauer Emge and see Chiapter 6)

persistence of adipose tissue cells in the tumours (Fig 64) and the metaplastic development of cartilage or bone in the fibromatous component. This last feature which is common in the canine tumours is rare in the human ones, Cheatle and Cutler saw it in only two cases, and I have seen it only once



Fig. 57 —Intra canalicular fibro adenoma with hyalinization of connective tissue from a woman of 28 (> 50)

Occasionally, mucinous change in the fibromatous tissue is prominent enough to give it a slimy feel, a bluish colour in haematorylin stained sections and meta chromatic staining properties with polychrome dyes, the name "myxofibro adenoma" is then appropriate Nicholson, Dawson, Geschickter and Lewis, and others have shown that fibro adenomas participate in the mammary changes of pregnancy and lactation Calcified spherules occur in the epithelial spaces of some of the old dense fibro adenomas

(e) Giant fibro-adenoma

Valuable reviews of the large soft or cystic fibro adenomas sometimes seen in the middle aged or elderly have been published by Lee and Pack (1931) and Owens and Adams (1941) who also cite Johannes Muller's classical and excellent account of these growths (1838) under the title "cystosarcoma phyllodes'. These tumours develop from small pre existing fibro adenomas of the usual type—they often enlarge slowly for several years and then may suddenly start to grow more rapidly. They have often attained a huge size, the average weight in the cases reviewed by Lee and Pack was 7½ lbs, and Mackenzic saw a tumour of 35 lbs. They are well circumscribed lobulated and often cystic, and they distend the skin and may suffer accidental ulceration, infection and fungation. But in the great majority of cases they are non invasive, non metastasizing tumours, with good prognosis following surgical removal

Microscopically the bulky masses of polypoid and cystic growth show luxuriant fibro adenomitious structure, usually of the intra canalicular type, and the fibro matous component often shows prominent myxomatous changes and cellular areas of sarcomatous appearance Infrequently, the epithehum lining the clefts

of epithelial and connective tissue vary greatly Adenomas, with ducts and aem forming the bulk of the tumours, seen usually in young people, are rare. Cheatle and Cutler give 4 examples Usually the fibromatous tissue exceeds the epithelial in bulk. The latter may be very scanty and the tumour little short of pure fibroma Proof of the purely fibromatous character of a breast tumour therefore requires very thorough search of many parts for the possible presence of epithelial elements I myself have not yet encountered a pure fibroma

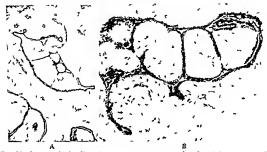


Fig. 56 —Intra-canalicular fibro adenoma compression atrophy of epithelium (A \times 40 B $\,$ 496)

Fibro adenomas which appear during puberty or adolescence often show a structure closely similar to that of the normal breast issue of the same age—and "frequently no histological evidence of a capsule is present even when, to the naked eye the defined tumour area suggests an easy—shelling out—(Dawson) Perhaps then no sharp distinction is possible between the rare diffuse mammary hyperplasias of adolescence and the commoner localized fibro-adenomas of the same period

(u) Intra canalicular structure—This arises by proliferation of the sub-epithelial tissues in a coarsely papillary pattern with invagination distortion and distension of the duets. Plane sections show to the naked eve a laminated appearance like sections of a crinkled cabbage and mero sections reveal the complex dove tailed shapes and interlocking of the branching convoluted parts (Figs 55 and 56). The epithelium elothing the fibromatous projections often suffers atrophy by stretching or compression and it sometimes disappears in places, leaving a raphe like junction of adjacent connective tissue papillae (Fig 56). During their early growth the tumours show the same delicate loose-textured fibromatous tissues as in the peri canabicular type—but old timours often show condensation and hyaline change of the connective tissue (Figs 57 and 58)

Unusual structural features of fibro adenomas include the presence of smooth muscle fibres in the connective tissue (Cheatle and Cutler) the inclusion and

(f) Malignant change in fibro adenomas

While most huge fibro-adenomas—even those of rapid growth and with suspiciously cellular areas—are benign in that they fail to invade neighbouring tissues or to metastasize, occasional tumours of this kind prove to be malignant Almost ilways, the malignant change involves the connective tissue component, which shows anaplastic cellular growth with plentiful mitotic figures, from which recurrence or metastasis ensues. White (1940), however, described a case in which extensive recurrence and metastasis followed removal of a large rapidly growing tumour of 2 years duration in a woman of 34, and his Fig 7 suggests that the pulmonary metastases may have contained epithelial components as well as sarcomatous growth, but no descriptive details are given

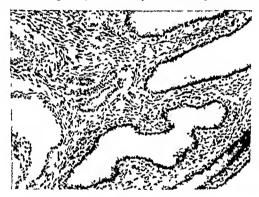


Fig 59 -Case II Giant fibro adenoma (× 120)

Carcinomatous change in a fibro adenoma, if indeed it ever occurs, must be extremely rare. It was not observed in the extensive experience of breast tumours of either Cheatle and Cutler or Dawson. Carcinoma and fibro adenoma may coexist in one breast, as in Cases VIII and IX below and carcinoma may invide a fibro adenoma. Tudhope described an unusual tumour which contained different areas of fibro adenomatous, carcinomatous and apparently streomatous structure together with the formation of cartilage and osteoid tissue by metaplasa of the stroma. He believed, possibly correctly, that the carcinoma had arisen from the epithelium of the fibro adenoma, so that this case may exemplify the extremely rare event of conversion of a fibro adenoma into a composite carcino sarcoma by simultaneous malignant change of both components. Budd and Breslin also studied an unusual composite tumour of the breast region, this had been present for 28 years and had grown actively only recently, microscopically it consisted of mingled active circinoma and osteogenic sarcoma. Mallory 5

and cysts shows squamous metaplasia in parts The following 3 cases illustrate many of the characters of these tumours

Case I — A married woman aged 77 had had a slowly enlarging tumour of the LΩ breast for 40 years at had recently become inflamed and ulcerated. Examination showed replacement of the breast by an irregularity hemispherical lobulated tensely cystic tumour

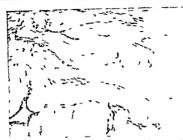


Fig. 58.—Fibro adenoma from an elderly woman showing hyalimization of connective tissue and atrophy of epithelium (\times 120)

25 centimetres in diameter with an infected fungating area on its lower surface. Simple mastectomy was performed, with a good result. The tumour weighed 9 lbs, and it had the structure of a simple fibro adenoma mainly of per-cansicular type with abundant not very cellular connective tissue. The patient died of pneumonia 4 months later necropsy showed no residual or metastatic growth, but a large papilliferous multilocular ovariant systadenoma was present.

Case II (Dr. Ian Pender's case)—The patient was a multipara aged 45 who had breast fed her children and had had no previous breast trouble and whose menstrual instory was normal except that the menses had not commenced until the 18th year Following a moderately severe blow on the left breast in March 1937 enlargement of the breast was noticed in May this intereased rapidly and radical amputation was carried out in October 1e. 5 months after the tumour was first noticed. The patient remained well several years later. Nuled ever examination showed a well-defined rounded remained well several years later. Nuled ever examination showed a well-defined rounded remained with the cut surface of which had the appearance of a soft oedematous fibro aderoma. The remaindur of the breast tissue and the availlary contents appeared normal. Histology (Figs. 59: 61)—The structure is that of a fibro adenoma mainly intra-canalicular but partly pere-canalicular in pattern. The epithelium luning the irregular glandular spaces consists of plump cubical or columnar cells which show a moderate number of mitoses. The connective tissue is very cellular in most places consisting of large fusiform cells many of which show mitotic figures. Collagen fibres are plentiful in some areas but almost absent in others.

Case III (Mr. Balcombe Quach, s. case)—A married woman under 40 years of age had noticed a small lump in the breast for 2 years. In this had grown rapidly in the last 6 months The breast was amputated. The tumour was well-defined rounded 10 centimetres in diameter with a cut surface that of a soft fibro-adenoma. First fibro-adenoma with intra-canalcular and pen-canalcular patterns in about equal proportions. The connective tissue is of moderate cellularity in most parts, and ome mitoses are seen in the cells Islands of adipose tissue cells have been incorporated in the peripheral parts of the tumour (Fig. 61).

and their sareomatous conversion. The experiments prove conclusively the correctness of the view long held by many histopathologists, that the connective tissue component is not merely a stroma to the epithelium but possesses neoplastic properties of its own, ie the tumours are genuinely mixed tumours properly designated "fibro adenoma" when benign and (usually) "adeno-sarcoma" when malignant. In the mammary fibro adenomas of dogs, sarcomatous change may

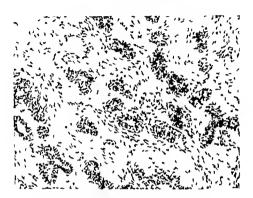


Fig 62 - Case III Giant fibro adenoma (x 120)

supervene in the metaplastic bone which the tumours often contain, and ossifying metastases may develop Schlotthauer and Thurber described an unusual example of osteogenic sarcoma of a dog's breast with osteoid metastases in lymph nodes, lungs, heart and kidney

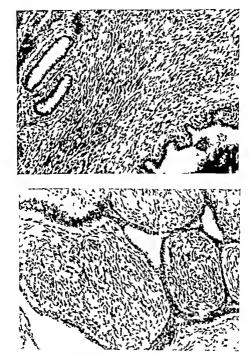
DUCT PAPILLOMA AND PAPILLARY CYSTADENOMA

Papillary growths of the breast like those of most other regions, cannot be sharply separated into beingn papilloms and papillary careinomas. All transitions occur between solitary or multiple localized slowly growing highly organized papillomas of main duets, and poorly organized active papillary growths associated with, and showing obvious transitions to, invasive careinoma. The present section deals only with the former, the endless permutations between this and the latter can be left to the reader's imagination.

(a) Age and sex incidence

Most simple papillomas are seen in young women, they are rare in children or in subjects over 55 years old Papillomas of the male breast are extremely rare

opinion was that an old fibro adenoma had long been present and that carcinoma and sarcoma had supervened in it, and this seems the most likely interpretation



Figs 60 and 61 -Case II Giani fibro-adenoma (x 120)

Chapter 6 discusses the interesting way in which study of the transplantable fibro adenomas of rats has shed light on the composite nature of these growths

multiple, and that transitions from cystic hyperplasia to papilloma formation could often be traced Single papillomas were usually in the main ducts near the inpple Multiple papillomas were usually unilateral, but occasionally bilateral, they might be very numerous—150 or more, and they might affect the whole extent of a duct and its tributaries. Cheatle and Cutler apitly likened this condition to papillomatosis of the colon, both as regards the wide extent of the epithelial field affected and the proneness of the papillary growths to become carcinomatous

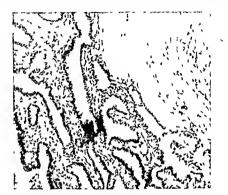


Fig. 65 -- Multi radicular papillary growth in a cystic duct (× 120)

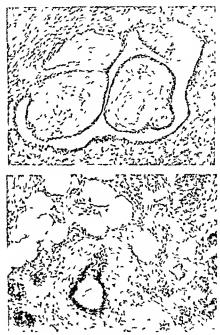
These observations have an obvious bearing on surgical treatment, they support the view that mastectomy is preferable to local excision of papillomas or papilliferous cysts. When local removal only is undertaken, the surgeon unaware of the pathological state of the rest of the breast, not seldom leaves behind a field of tissue of great or small extent in which similar or more serious neoplasia may manifest itself later. The regular performance of mastectomy—not necessarily the radical operation—for duct papillomas which appear clinically to be solitary and localized may sacrifice some breasts needlessly but it will certairly save other patients from the subsequent recurrence of pupillomas or of carcinoma

(d) Structure

Duct papillomas may be sessile or stalked, and the stalked ones may be uni radicular or multi radicular more often the latter. Uni radicular growths may have a simple villous structure, but fenestrated or reticular formations are more common (Fig. 65). Simple distension of part of a duct by a single growth is less frequent than the formation of irregular papilliferous clefts and cysts. Papillary cystadenoma' is a name sometimes applied to the latter condition

(b) Papillomas in animals

The only animals to show mammary papillomas frequently are dogs in which papillary growths usually along with cystic changes fibro adenoma or careinoma are quite common. Feldman mentions papillomas of the teat duets of cows



Ties 63 and 61 - Case III Giart fibro-adenoma (e 10

(c) Site and mode of origin

Cleate's studies of whole bresst sections revealed that duct papillomas were present more frequently than clinically suspected that they were often

That during recent years there has occurred a real increase in the incidence of bre ist cancer in Great Britain and the United States of America, independently of the increasing average age of the population, will be pointed out below when age incidence has been discussed

(b) Clinical and pathological records

Sufficiently large series of unselected hospital cases show rough general agreement with mortality statistics is regards the relative frequency of mammary, uterine and other common tumours. Thus, the Annual Report of the British Empire Cancer Camping for 1940 contains a review of 7,872 pooled cases of malignant disease of both sexes from London hospitals, these included 1,345 cases of mammary cancer and 639 cases of uterine cancer, a ratio of approximately 2 to 1. My series of 1 060 necropsy cases of carcinoma (Table V, Chapter 5) included 92 cases of mammary carcinoma and 49 cases of uterine carcinoma—again a ritio of about 2 to 1. The total number of female cases in my series was 425 so that carcinomas of the breast and uterus constituted respectively about 22 and 12 per cent of all female carcinomas, while carcinomas of the large intestine and of the stomach numbered 76 and 70 cases (18 and 16 per cent) respectively Minimary carcinoma was thus the commonest malignant growth in women

For populations without proper mortality statistics, clinical and pathological records are the only useful means of estimating the relative frequency of breast eancer and other tumours. Amongst the best studies of this kind are those of Nath and Grewal, in India These showed that, while mammary, uterine and other cancers varied in their relative proportions in different districts and racial communities pooled figures showed a decided preponderance of uterine tumours Cancer of the female genitals (mainly of the uterus) constituted 365 per cent, and cancer of the breast 242 per cent of all female cancers, in Hindus the percentages were 390 and 224, in Mohammedans 263 and 305 and in other castes 354 and 261 These figures are borne out by those of khanolkar of Bombay, who, in a series of 2,880 microscopically verified cases of carcinoma, saw 300 cases of carcinoma of the cervix of the uterus and 159 cases of carcinoma of the breast, the numbers of cases of these two diseases in Hindus were 229 and 75 respectively, in Moslems 20 and 23, and in Parsees 14 and 27 Quinland and Cuff's collection of 300 cases of earcinoma in negroes included 112 of the uterus and 64 of the breast

(c) Sex incidence

In England and Wales in 1938, there were 7,218 female deaths and 60 male deaths from cancer of the breast In Victoria, in the decade 1933 1942, 2,518 women and 26 men dued of this disease Many other recorded series also, e.g. those collected by Hoffman, have shown breast cancer in females to be about 100 times commoner than in men are described later.

The properties of male mammary carcinoma are described later.

(2) Age incidence

(a) Ages at death

The mortality figures of England, United States of America and many other countries show closely similar age distribution curves for mammary cancer

Sessile multiple and irregularly cystic growths are more likely than those of a simpler structure to be associated with or to show transitions to carcinoma

CARCINOMA OF THE BREAST

(1) Frequency

(a) Mortality rates and race incidence

Because the diagnosis of mammary cancer in its late stages is in most cases obvious the mortality figures of most civilized countries may be accepted as fairly reliable. Its frequency as a registered cause of death differs decidedly in different countries and the differences are too great to be accounted for by diversity of age and sex composition of the populations (Table I)

TABLE 1

MORTALITY RATES FROM BREAST CANCER IN VARIOUS COUNTRIES IN 1930 (DESCENDING ORDER)

ALONG WITH BIRTIL RATES 1930 AND 1910

(From Bogen 1935)

| | | | | Breast | cancer | Birth rates per 1 000 | | |
|------------------|-----|---|---|---------------------------------------|--------------------------|-----------------------|------|------|
| Coun | try | | ŀ | Death rates per 100 000 females | Percentage of cancers | 1 | 1930 | 1910 |
| England and Wale | 5 - | - | | 29 2 | 191 | 1 | 163 | 23 8 |
| Scotland | ~ | - | - | 23 4 | 150 | | 195 | 26 1 |
| Denmark (urban) | - | - | ~ | 22 6 | 173 | t | 187 | 256 |
| New Zealand - | ~ | - | ~ | 22 4 | 200 | | 188 | 26 0 |
| Switzerland - | | - | _ | 21 2 | 110 | | 172 | 239 |
| Netherlands - | | - | - | 193 | 13 8 | | 23 1 | 28 2 |
| USA | | - | ~ | 17 6 | 15.1 | | 18 9 | 24 9 |
| Australia | _ | - | - | 16.5 | 17.2 | 1 | 199 | 28 1 |
| Ireland | - | - | - | 160 | 160 | | 20 2 | 22 6 |
| Norway | - | ~ | - | 14.5 | 7.4 | | 24.5 | 25 3 |
| Canada | | | - | 11.5 | 176 | | 24.5 | 26 6 |
| Italy | - | - | - | 60 | 10 0 | | 26.2 | 317 |
| Spain | | ~ | - | 36 | 70 | | 290 | 31 2 |
| Ceylon | - | - | - | 36 | 76 | | 39 0 | 38 1 |
| Japan | ~ | - | • | 18 | 30 | | 32 4 | 34 1 |
| Chile | _ | - | - | 12 | 20 | | 39 8 | 370 |

Whereas in the earlier years of the present century deaths from uterine careinoma exceeded those from mammary careinoma in England and Wales. United States of America. Australia etc. (see Chapter 31) the reverse now obtains. Thus, of 35 913 female deaths from cancer in England and Wales in 1938. 7 218 (20.1 per cent) were from mammary cancer and 4 519 (12.6 per cent) from uterine cancer. Of which 2 518 (20.3 per cent) were from mammary cancer and 1 656 (13.3 per cent) from uterine cancer. In English and Australian women the recorded deaths from mammary carcinoma exceed those for every other organ including the stomach. In many European countries most notably the Scandinavian countries and Hollind. Tecorded deaths from gastric cancer greatly exceed those from mammary cancer. The remarkably low death rates recorded for mummary cancer in Italy. Spain Japan and Chile merit further study.

breast cancer to total cancer deaths has also shown an upward trend, e.g. in U.S.A. this rose fairly steadily from 7.3 per cent in 1900 to 9.5 per cent in 1930 (Bogen), and this in spite of the fact that, while improved diagnosis must have caused an increase in registered deaths from internal cancers, breast cancer could have shared but little in this improved diagnosis. It appears clear then that there has been a real increase in the prevalence of breast cancer, quite apart from its increase because of ageing of the population

(4) Spontaneous or experimental mammary careinoma in animals

Mammary earcinoma is of course very frequent in mice, in which, by selective inbreeding, strains of either high cancer or low-cancer incidence have been The experimental study of breast cancer in mice has been outlined in Section IV of Chapter 4 Bonser (1945), studying the evolution of mouse mammary cancer, found that this, like human cancer, arises gradually and multi focally, but that it usually begins in the acini and that the milk factor acts mainly This difference from human cancer, which usually begins in the ducts, raises the question whether a milk factor exists in the human subject

Dogs frequently develop carcinomas of the breasts (see Chapter 6), and these show many points of similarity to human tumours. They often supervene on cystic hyperplasia and all transitions between this and papillomas and carcinomas are seen. Multifocal origin in one or several breasts often occurs. In a lactating dog's breast, Dawson (1935) saw lactation in a papillary carcinoma Carcino matous change in fibro adenoma is not rare. Study of the reproductive and lactational history of dogs with breast tumours is needed

Carcinoma of the breast is not common in other mammals, but occurs in rats cats horses swine cows, sheep rabbits and guinea pigs

(5) Reproductive and lactational history in relation to mammary carcinoma

Since the breast is subject to hormonal control related to sexual and repro ductive functions on a priori grounds we might suspect disturbances of these functions to play a major part in the genesis of breast cancer The results of much statistical and some experimental work have left no room for doubt that this is indeed the ease. Only some of the evidence on this question can be referred to here for further details see the classical papers of Janet Lane Claypon (1924, 1926 and 1928), and the confirmatory papers of Wainwright and Bogen

(a) Marital state

It has long been recognized that single women are more liable to mammary cancer than married women The mortality rates in England and other countries show an excess of deaths among the unmarried when due regard is paid to the proportion of single women in the general population Lane Claypon's figures from the surgical literature (1924) showed that in England 15 per cent of the female population over 40 years of age were single, but 22 per cent of the breast cancers were from single women, in America the corresponding figures were 8 and 18 in Denmark 14 and 30 The Registrar General's analysis of deaths in 1930 32 showed the death rates of mammary cancer to be markedly greater for single than for married women in all age groups over 35

Representative of these are the figures in Table IV, Chapter 5 These show that fatal mammary cancer is infrequent under the age of 35 that a rapid rise in the number of deaths occurs in the fifth decade and is maintained in the sixth, that more than half the total deaths take place between 45 and 65 and nearly three-quarters of them between 45 and 75 and that the mortality rates for people of different ages show a continuous rise from youth to old age

(b) Clinically recorded ages

The studies of Lanc Claypon, Wainwright and others have shown that distribution curves of clinically recorded ages—ic ages of operation or of onset of symptoms—attain their peak at ages 5 or more years earlier than the mortality curves. The peak occurs early in the sixth decade or in some series (e.g. that of Pack and Le Fevre) near the end of the fifth decade. The difference between the curves for fatal and clinical series in this respect is accounted for by the mean duration of about 3½ years for untreated cases and the markedly prolonged average expectation of life from adequate surgical treatment especially in early cases (See Lanc Claypon.)

Mammary cancer is rarely seen in patients less than 30 years old, but most surgeons and pathologists will recall instances. Velpeau saw the disease in a girl of 17 and in several other women under 30 and more recent records of such cases include those of Wildbolz and of Sears and Schlesinger who reported a carenoma in a child of 10 My 92 necropsy cases included 2 women under 30 aged 23 and 29 Haagensen and Stout recorded 18 patients under 30 years of age, the voungest 22

(3) The increase of mammary cancer

The effect of changes in the age distribution of populations on the incidence and age distribution of mammary cancer is well shown in Table II

Table II

Trind of Deaths from Breast Cancer in the U.S. Registration States of 1910 (from Bagen 1995)

| | | | | | 1911 | 1920 | 1930 |
|-----------------------------|--------|----|---|-----|------------|------------|------------|
| Population | _ | _ | | - | 48 295 860 | 56 080 552 | 66 442 606 |
| Deaths from breast cancer | - | - | - | - | 3 610 | 4 900 | 7 409 |
| Rate per 100 000 (all ages) | - | | - | - | 75 | 88 | 11 2 |
| (15-44) | - | - | - | - | 29 | 3 1 | 3.6 |
| (45-64) | | - | ~ | - | 22 t | 25 6 | 340 |
| (over 65) | _ | - | - | - | 498 | 55 0 | 616 |
| Percentage of population ov | er 45 | - | - | - | 209 | 240 | 25 6 |
| Percentage of breast cancer | over . | 45 | - | - 1 | 80.6 | 82.7 | 84.4 |

This table shows that in the United States of America (and the same applies to England and many other countries) the crude mortality rate of breast cancer has risen markedly during recent years and that this rise is due in large part to the ageing of the population. That it is not wholly due to this however is shown by the upward trends of the standardized or age specific rates also. The ratio of

Similar statistical studies of the suckling habits of the Japanese, Chihan, Spanish, Italian, and other women with relatively low incidences of breast cancer, are needed

That premuture weaning can engender breast tumours in mice and rats is shown by the experimental results of Bagg and others cited in Chapter 4

(e) The social distribution of cancer

The Registrar General's figures of cancer deaths in England and Wales (1938) indicate a definitive class gradient for mammary erneer. For this purpose each occupation was assigned to one or other of five descending social classes, and married women were grouped according to the social class of their husbands Expressing the cancer morthlity in each class as a percentage ratio of the general average that for cancer of the breast in married women showed a progressive decrease from Class I to Class V as follows, 138, 116 103 84, 82. Among single women the class gradient for breast cancer was less pronounced. In general then, women of the upper social classes in England are decidedly more subject to mammary cancer than those of the lower classes. It is quite probable that this is due to reproductive and lactational differences, as already suggested in the preceding section, the upper classes living less "natural" lives as regards reproduction and lactation

(f) Conclusions

From the foregoing discussion the main facts to emerge are

(i) Single women are more hable than married women to develop breast

(u) The liability to breast cancer in child bearing women is inversely related to fertility, and communities with a low (and especially a falling) birth rate show a high rate of breast cancer

(iii) There is evidence, statistical as well as experimental, to show that failure to suckle, premature weaning and possibly other errors of

lactation play a part in the genesis of mammary cancer

(iv) Women of the upper soeral classes in England are more hable to breast

It seems safe to conclude then that the women least liable to mamming cancer are those who have borne and normally suckled several children, while the most liable are those who have not borne children, or who, having borne children have failed to suckle them. Thiwarted reproduction and thiwarted lactation predispose to cancer, normal reproduction and lactation are the prophylactics. With good reason we may strongly suspect that the high and increasing prevalence of breast cancer in the Western civilized peoples is related to the "unnatural" reproductive life of a large proportion of the people.

(6) Heredity and mammary carcinoma

It is possible by close inbreeding to obtain strains of mice of either very high or very low incidence of mammary cancer, but these results are not generally applicable to human communities in which such close inbreeding rarely occurs. Nevertheless, as mentioned in Chapter 5, there is some statistical evidence that the incidence of mammary cancer in female relatives of patients with manumary.

(b) Menstrual history

Careful comparisons of large series of cases of mammary cancer with proper control series of non-cancerous subjects (Lanc Claypon 1926, Wainwright, 1931) showed no significant difference with respect to the age of onset or cessation of menstruation the total duration of menstrual life or disturbances of the menstrual cycle or the menopause Bonser (1935) observed that the incidence of breast tumours in mice was not demonstrably related to the characters of the oestrous cycle

(c) Ferulty

Lane Claypon's comparisons of cancerous and control series of married women showed an unmistakable difference of fertifity. Even when allowance was made for eases in which the disease itself may possibly have diminished child bearing capacity, it was found that women who ultimately developed main mary cancer bore 22 per cent fewer children than the control cases. In the control and cancerous series the average numbers of vable children per married woman were 4.97 and 3.53 a ratio of 1.4 to 1. Wainwright's American series showed a ratio of 2 to 1. The average age at marriage was also significantly lower in the control series than in the cancerous series, in both England and U.S.A.

Confirmation of the inverse relationship of fertility and the liability to mammary cancer is afforded by Bogen so observation of a striking parallelism between low brith-rate and high breast cancer rate. Thus England which in 1930 headed the list for mortality rate from breast cancer had a birth rate of 16 3 per 1 000, while at the bottom of the list were Japan and Chile with very few breast cancers and birth rates of 32 4 and 398 respectively. Moreover, and perhaps even more significantly countries high in the list of breast cancer showed a diminishing birth rate between 1910 and 1930, e.g. in England from 23 8 to 16 3 while countries with little breast cancer showed no great changes in their relatively high birth rates between those years e.g. Japan's birth rate in 1910 and 1930 were 34 1 and 32 4 and Chile's 37 and 39 8. A similar inverse relationship obtained between breast cancer rates in the various States of U.S.A. in 1930 and their birth rates in 1900. Bogen concluded from these and other observations that child bearing and lactation constitute a natural protection against the subsequent development of breast cancer.

(d) Lactation

Many statistical and clinical workers have laid stress on errors of lactation as a cause of breast cancer. Thus Leaf (cited by Lane Claypon 1924) in a careful analysis of 100 cases of breast cancer found lactational errors in the majority. In her 1926 report Lane Claypon found that complete failure to suckle and the habit of suckling for a very long period were both more common in the cancer series than in the control series. Thus in the control series mothers failed to suckle 74 per cent of their children while in the cancer series 146 per cent of the children previously borne had not been suckled. In her 1928 report on a further series of cancer cases, Lane Claypon found a history of failure to suckle in an even higher degree namely for 19.1 per cent of the children. In Wainwright a American series 28.2 per cent of married women and widows with mammary cancer had never lactated, while the percentage in the control series was 15.7.

the luming of the ductules are either reduced by the bulky epithelium or enlarged into small or large cystic spaces. A frequent type of lining seen in cystic structures consists of large cosmophil epithelial cells. This type of epithelium, which has been thoroughly studied by Dawson (1932), has often been regarded, erroneously, as sweat gland tissue. It is present in almost all cystic breasts and in many cancerous breasts also, but there is no evidence that it is ever the origin of carci Cheatle and Cutler regard this type of conthelium as always of acmar origin, and hold also that all large mammary cysts arise from acini I join Dawson in dissenting from this view, I am unable to distinguish as sharply as Cheatle does between duct and acmar structures in cystic hyperplasia. In my experience, eosinophil epithelium can appear in other acmi (ductules) or ducts, and large cysts can develop from either Microscopically, the fibrosis accompanying the epithelial hyperplasia consists in the earlier phases of rather loose textured fairly cellular tissue, but around older atrophic epithelial structures and cysts it becomes more densely fibrous Increase in the periductal clastic tissue is frequently present Inequalities in the density of the connective tissue, along with cysts and the more bulky foci of hyperplastic epithelium, give the breast its "lumpiness" Collections of lymphocytes and other inflammatory and phagocytic cells are not infrequent in cystic breasts, but these are secondary to degenerative changes

(c) The nature of cystic hyperplasia

It is now generally accepted that 'chronic mastitis" is a misnomer and should be discarded. Cystic hyperplasia is clearly due to disordered hormonal control of the breast in which oestrogen excess appears to be the principal factor. This is no place to consider at length all the evidence for this at must suffice to recall that the structure and function of the breast depends on hormonal (especially ovarian) control, to point to the structural changes just described which are clearly non inflammatory and essentially hyperplastic in character, and to note that the changes of cystic hyperplasia as seen in the human breast can be reproduced experimentally in animals by oestrogen excess (Burrows Bonser)

(d) Carcinomatous change in cystic hyperplasin

Any competent pathologist who has examined a considerable number of surgically removed breasts will find it difficult to remain patient with those surgicons who deny the pre cancerous potentialities of cystic hyperplasia. This denial is based on two misconceptions. One of these is due to the persistent use of the fallacious term 'chronic mastitis', under which many surgeons continue to group all lumpy breasts irrespective of their histopathology. Hence as Cheale points out they fail to distinguish the innocuous non cystic lobular type of hyperplasia ("mazoplasia" or "adenosis") which is frequent in adolescents and young adults and which often resolves, from the permanent cystic type of hyperplasia which develops usually after the age of 30, and is "a lesson of great menace.' The other cause of disagreement between surgical and pathological opinion regarding the pre cancerous proclivities of cystic hyperplasia is failure to distinguish between clinical and pathological diagnosis of this condition. Many womea with cancerous breasts give no history of any clinically detected previous breast disease, yet examination of the excised organ shows widespread hyperplasia and

cancer exceeds that in the general female population, nearly ten fold in Dutch women, according to Wassink

There are seen occasional instances of "cancer families" in which several sisters or other near relatives suffer from mammary carenoma. Said Velpeau in 1853. I have seen families in which three sisters daughters of one mother who had died of cancer of the breast, were attacked between the ages of 30 and 40 years with cancerous tumours in the same situation. Surgeons of to day encounter similar families (Handley, 1938, Wood and Darling, 1943). In the family reported by Wood and Darling cases of bulateral mammary cancer occurred in four generations, including three sisters in one generation. The growths appeared at an average age of 32, it carlier than usual and one patient in the fourth generation developed the disease at the age of 18

(7) The relationship of carcinoma to cystic hyperplasia

"Chrome cystic mastitis"—the misnomer most commonly used by surgeons, Brodie s benign cystic disease", Schummelbusch s disease 'Reclus's disease 'Aschoff s cystic mastopathy , Prioran s' polycystic breast degeneration', Cheatle s "cystiphorous desquamative epithelial hyperplasia —these are some of the synonyms which have been applied to the variants of a change which is sufficiently designated by the simple name 'cystic hyperplasia Because cystic hyperplasia of the breast is a frequent precursor of carcinoma, it is necessary to summarize briefly its main characters

For further details consult keynes Charters, and Cheatle and Cutler (1931)

(a) Naked eye appearances of cystic hyperplasia

Common to all forms of the disease are visibly increased fibrous tissue the presence of cystic spaces large or minute and irregularities of consistency apparent to the palpating finger and visible on the cut surface of the tissue. These irregularities are due to cysts to unequal fibrous to hyperplastic enlargement of groups of lobules, or as the microscope sometimes unexpectedly shows to early multifect of cardiance. The changes may be universal throughout the breast or may affect only a part or parts of it. Cysts may be large, and single or multiple, or they may be tuny scattered and inconspicuous. Their contents may be clear and watery or thick and creamy, that of the large cysts often being clear, while that of small cysts and dilated ducts is often creamy and expressible from the cut surface like worm casts.

(b) Microscopical changes in cystic hyperplasia

These involve the ducts acim (better called "ductules", as Dawson points out) and connective tissues. The small terminal ducts are more affected than the large main ducts. The duct epithelia show proliferation, desquamation especially of large pale degenerating cells resembling colostrum corpuscles banking up of cells in masses, and papillary formations and the duct lumina are distended by the desquamated cells and by cell debris. Epithelial hyperplass in ductules distends these increasing their bulk and so causing their packing together in prominent lobules around the small terminal ducts. The multiplying cpithelial cells are enlarged packed together and may assume papillary formation, and

The possibility that the relationship between cystic hyperplasia and carcinoma of the breast may be due in part to the formation of carcinogenic substances in retained secretions has been suggested by Cheaile, Keynes, Charteris, Cappell, and myself (in Section IV of Chapter 4)

The following personally studied cases illustrate the supervention of multifocal carcinoma in eystic hyperplasia, as well as other important features of mammary carcinoma (See also Figs 68 70)

Case IV -A single woman of 26 had had a lump in the upper outer quadrant of the right breast since the age of 12. It had remained unaltered until recently, when following a blow on the breast it had increased in size and become painful. Examination showed a hard area 2.5 centimetres in diameter adherent to the skin. Radical mastectomy was performed (September, 1937) An area of carcinoma 3 centimetres in diameter lay in the peripheral part of the upper outer quadrant. At another part of the periphery there was a second carcinomatous area 9 millimetres in diameter. The remainder of the breast showed firm but pliable fibrosis and many scattered small nodular areas and small cysts From naked-eye examination this tissue was not thought to be cancerous but to be the seat of lobular and fibrous hyperplasia. To our surprise however microscopical study showed that the entire breast contained focal or diffuse areas of early carcinoma clearly arising from and replacing previously hyperplastic lobules or ducts (Fig. 66). The two areas of macroscopically obvious carcinoma were clearly only the most advanced and oldest regions of neoplasia in a breast which was in process of similar change in toto. In September 1939 the patient complained of pain in the back and skiagrams showed partial destruction of the 7th dorsal vertebra Deep X ray therapy was followed by improvement, and the patient married in 1940 In January 1941 a 3 months' pregnancy was terminated for prophylactic teasons. In March 1941, pains in the back were still present The left breast appeared normal

Case V—A married woman aged 42 the mother of 2 children had noticed a lump in the left breast for 6 weeks. Examination showed a mass $5 \times 4 \times 15$ centimetres in the upper inner quadrant unattached to skin or muscle and slight general lumpness of the rest of the breast. The right breast also was "knotiv, with chronic martitis" in June 1936 simple mastectomy of the left breast was performed. sections showed active carcinoma supervening on widespread hyperplastic changes. Year therapy was given and in November 1936 the patient remained well. In November 1937 she complained of a lump in the right breast noticed for 2 weeks. Eximination showed chronic mastitis with 7 cyst in upper outer quadrant. The treatment adopted was simple mastectomy followed by deep X ray irradiation. Section of the breast showed it to consist largely of plant fibrous tissue contaming many small cysts and dilated ducts with milky contents and many discrete hard shorty patches. Sections from various parts showed cystic hyperplasia with multiple early carcinomations areas.

Case VI—The seemingly ill advised haphazard treatment of this patient wa due to her having attended 4 different clinics at 2 different hospitals without disclosing this to the several doctors concerned. She was a sterile married woman of neurotic type who first attended hospital in 1935 at the age of 31, complaining of a lump in the right breast. This was a will defined rounded mass 15 centimetres in diameter which was diagnosed fibro adenoma. and was enucleated Although naked-eye section of the tumour appeared to confirm this diagnosis incroscopical study unexpectedly disclosed a localized carcinoma. The patient then transferred herself to another hospital where in a gynaecological clinic set received prolonged internutient treatment with oestrogene hormones. In November 1939, the left breast was amputated and sections showed undespread cystic hyperplasia with early multifocal carcinoma. In June 1941, chronic masture of the right breast was diagnosed. In 1942 this breast was removed and also showed extensive cystic hyperplasia and multiple areas of well-established carcinoma. There were no signs of recurrence in January 1943.

sometimes multicentric carcinomas which were undetected clinically For every case in which a clinical diagnosis of cystic hyperplasia antecedent to carcinoma has been made there are a score in which a pathological diagnosis of this sequence is clear from adequate examination of the amputated breast (Lane Claypon, 1926)

The danger of cystic hyperplasta in the middle aged woman has been fully discussed by Cheatle (1920 and 1925), Keynes Lane Claypon Charteris, Cheatle and Cutler Handley, Warren, Muir Dawson (1943) and many others. The proportion of cancerous breasts which show definite transitions from hyperplastic changes to carcinoma is estimated variously by different workers. Cheatle and Cutler placed it at 20 per cent but others including myself think this is an underestimate. For reasons already given it is impossible to determine even approximately what proportion of breasts with cystic hyperplasta may become cancerous

Caremoma supervening on hyperplasm is often multicentric or diffuse in origin arising from extensive reaches of one or more duets or even from the entire breast. Sometimes such tumours are bilateral, and should a middle-aged woman with evisic hyperplasm of both breasts develop caremoma in one, the risk of caremoma supervening in the other also is great enough to justify local mastectomy of the second organ. Dogs sometimes show simultaneous caremoma of all mammae, with striking examples of transition from widespread cystic hyperplasm to papillomatous growths and caremoma.

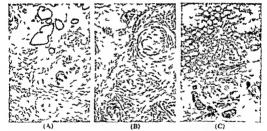


Fig 66 - Case IV A B and C are from widely separate parts of the breast (x 35)

It is not denied that some breast cancers are of localized origin and unaccompanied by significant changes in other parts of the organ. But purely local growths are much fewer than would appear from clinical examination only. Further microscopical examination of only one or two small sections of areas of obvious growth is inadequate to reveal the relationship under discussion and must lead to false conclusions regarding it. The more thoroughly the pathologist examines amputated breasts the more often he will discover the presence of cystic hyperplasia in association with carcinoma and of clear transitions from one to the other

duct obstruction might sometimes be causative in the human breast also, or might precipitate peoplestic change in breast tissue already prepared for it

Suppurative mastitis does not predispose to cancer, but transient non suppurative mastitis may possibly do so (Lane-Claypon) Tuberculosis and carcinoma occasionally coexist in the breast (Bundschuh), but the association is probably fortuitous. It is noteworthy that mammary tumours are very rare in cows, in which tuberculosis and other kinds of bacterial mastitis are common

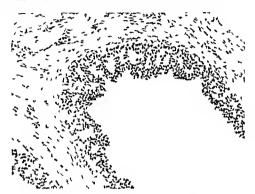


Fig 67 -Early intra ductal carcinoma in a large duct (× 120)

(9) Site and mode of origin

That breast carcinomas often arise from more or less extensive fields of prepared tissue will be clear from the preceding pages and from Chapter 7 Cheatle and Cutler grouped the tumours according to their origin as follow

(i) Carcinoma arising in the mpple—This comprises tumours of the main ducts in the hipple, and those of its condermal surface (see Paget's disease)

(u) Carcinoma arising in a localized part of a large duct—The most frequent form is papillary carcinoma, which may long remain confined within the duct as 'papilloma' or papillary cystadenoma before invasive properties appear

(iii) Carcinoma arising in a main duct and all its tributaries and acint—This forms a large irregular pyramidal growth with its base towards the periphery of the breast and its apex towards the nipple. It often shows all stages of caret nomatous change in progress and is a very fatal type

(iv) Carcinoma arising in terminal ducts and acim —This is the common

peripheral type of growth

(v) Caremona arising diffusely throughout most or all of the breast or of both breasts—This is a rare very fatal type producing a small firm breast with no single palpable focus of tumour sometimes accompanied by Paget's disease

Case VII —A woman aged 43 had noticed a lump in the right breast for 3 weeks. It was excised locally sections showed fibro adenomatous nodules amidst areas of extreme hyperplasia and one mall focus of intra duct carcinoma. Simple mattectomy was then performed and sections showed generalized cystic hyperplasia but no other breast and enlarged right auditary glands wen, felt. Left mastectomy was performed and the right avilla was cleared. The breast showed generalized cystic hyperplasia but he availtry glands showed three deposits of spheroidal-cell carcinoma.

Case VIII (Mr. John Kennedy's case)—In November 1941 a single woman aged 47 consulted her doctor with signs of a thyroid adnorma and thyroiovicosis and also a clearly carenomatous mass in the right breast with enlarged axiliary Jimph glands. Radical removal of the breast was performed section showed an area of obvious carenoma 4 centimetres in diameter and cancerous deposits up to 25 centimetres in diameter in the lymph glands. Microscopie examination confirmed these findings and showed also areas of cribriofirm carinoma in the dicts in other parts of the hyperplastic breast tissue. In December 1942 a lump appeared in the left breast which was removed. Section of the fixed organ showed wides persend fibrous change with scattered small cysts a deep-scated area of carcinoma. 2.5 centimetres in diameter and at the inner periphery of the hyperplastic breast tremote from the carcinoma a well defined encapsulated fibro actions. The continuence is diameter and at the inner periphery of the hyperplastic breast temote from the carcinoma a well defined encapsulated fibro actions. The performance of the properties of the properties of the properties of the hyperplastic breast temote from the carcinoma as well defined encapsulated fibro actions.

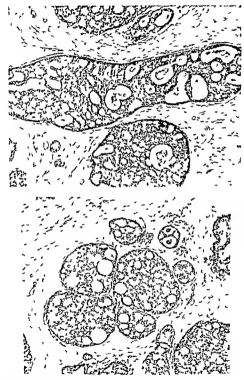
Care LV (Mr. A. J. Trinca a case)—The patient had tumours palpable in both breasts and blatteral radical removal was performed. Sections after haxion showed widespread hyperplasia of moderate degree in both breasts and 3 separate tumours as follow R. Breast. (1) An irregular mass 2.5 centimeters in diameter slightly addicent to the skin at the lower periphery microscopically spheroidal-celled and ad nocarcinoma (2) A well defined freely mobile mass 2.5 centimetres in diameter in the inner periphery affirst thought to be a simple fibro-adenoma but microsopically a focus of spheroidal celled careinoma accompanied by several small fibro adenomatous foot. L. Breat (3) An irregular hard mass in the upper outer periphery adherent to the pectoral fact microscopically densely scirrhous spheroidal-celled carcinoma. No tumour deposits were found in lymph glands on either side.

Case X (Mr. W. D. Upoins case)—In 1937 a sterile married woman had chrowing matitis which was symptomatically improved by administration of stithoestrol. In 1943 a small war like growth appeared on the right nriple and was removed by diathermy by a demiatologist. This recurred a few months later and was again removed by diathermy by a demiatologist. This recurred a few months later and was again removed by diathermy Subsequent heating was imperfect and a surgeon was consulted. He found evidence of bidateral chromic mastitis and some enlarged glands in the right axills and advised removal of the right breast showed a depressed puckered nipple some thickening of the periductal connective tissues and a few scattered small cysts up to 4 millimetres in diameter but no sign of any tumour. The axillary slands however contained large deposits of obtious growth. Microscopicallt the glands showed large deposits of active spheroidal cell earcinoma with some mucoud change. The nipple area was free of tumour Many sections of different parts of the breast showed microscopic foci of carcinoma chearly arising multifocally from hyperplastic ducts and widely infiltrating lymphatics no carcinomatous mass of a size visible to the naked eye was anywhere present

(8) The relationship of carcinoma to injury and inflammation of the breast

Injury is often blamed as the cause of mammary tumours but in most cases it is clearly only coincidental or series to draw attention to a tumour already present. However in view of the experimental results of Bagg and others on the part played by injury of ducts in the genesis of breast tumours in mice and rats (Chapter 4) we must admit the possibility that previous injury leading to

structure seen in carcinomas of the breast may be described conveniently in the following order



Figs 69 and 70—Details of the intra ductal growth shown in Fig. 68. Note the restriction of the tumour to duct confines, and its embriform pattern $(\times 80)$

(a) Intra-ductal types of growth-papillary, cribriform laciform and solid

The four quadrants of the breast are affected with very unequal frequency, the order being—upper outer upper inner, lower outer and lower inner quadrants. This is exemplified by the following grouping of sites in 640 amputation cases recorded by Haagensen and Stout.

| | | | Cases | | | | | | Cases |
|----------------------|---|---|-------|---------------|---|---|---|---|-------|
| Upper outer quadrant | ~ | ~ | 277 | Lower half | ~ | - | ~ | - | 15 |
| Upper inner quadrant | ~ | _ | 78 | Outer half | ~ | ~ | - | - | 35 |
| Centre | ~ | - | 74 | Inner half | ~ | ~ | ~ | ~ | 5 |
| Lower outer quadrant | ~ | _ | 51 | Entire breast | ~ | - | - | - | 15 |
| Lower inner quadrant | - | - | 28 | Unspecified | ~ | ~ | ~ | ~ | 15 |
| Upper half | - | ~ | 47 | - | | | | | |

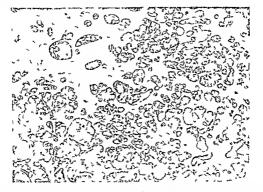


Fig. 68—Intra ductal carcinoma of cribinform type from a woman of 38. At age of 33 an area of cystic mastins was locally excised, she then remained well for 4 years when the growth here depicted was noticed. Four years after mastectomy a recurrent ulcerated growth was present. (x 8)

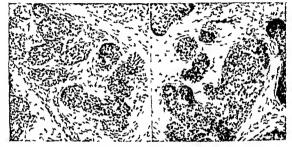
(10) Structure of mammary caremoma

Carenomas of the breast show a wide range of microscopical structure—from highly organized papillary or adenocaremomatous to diffusely cellular anaplastic growths. Quite commonly different parts of one tumour show different structural variants and terms such as comedo scirrhous' medullary' adeno." and simpley have only locally descriptive not classificatory, value. While individual tumours often show predominance of one or another type of structure the structure of a tumour is rarely uniform throughout. Histological sub divisions of mammary careinoma are arbitrary and, when they are based on single or few sections of each tumour they are often misleading. The main varieties of

These include the following

(i) Adenocarcmoma—Usually of simple actuar types, with either scanty or abundant fibrous stroma—less commonly of papillary and cystic types—(See also mucoid carcinoma below)

(1) Spheroidal cell carcinoma simplex—Often called also "alveolar" carcinoma consisting of solid clumps or strands of polyhedral cells set in a sponge work of stromal connective tissue (Figs 74 and 75). This tissue may be abundant and dense ('scirrhous' carcinoma), or scanty and delicate ("medullary" or 'encephaloid' carcinoma)



Figs 72 and 73 - Ductules distended by carcinoma (× 120)

(uu) Diffuse anaplastic carcinoma—Diffuse anaplastic carcinoma comprises the most disorderly rapidly growing forms of carcinoma simplex, ranging from the most cellular forms of the previous type (u) to completely diffuse pleomorphic or spindle-cell growths devoid of any histological signs of epithehal arrangement

It must be insisted again that these types of growth are not entities but merely variants of the entity mammars carcinoma and that the more thoroughly timours are examined, the more often individual timours are shown to have a range of structure including several of these variants. A broad parallelism obtains between the predominant type of structure of timours and their prognosis—(i), (ii) and (iii) denoting an ascending order of malignancy, but this is of little value in individual prognosis unless the particular timour has been examined very completely and has been found nearly homogeneous in structure

(c) Metaplastic types of carcinoma

These are not separate types either, but merely variants of the preceding types, showing aberrant differentiation or metaplasia of part of the cancerous epithelium in one or other of two ways

(i) Mucoid carcinoma—Mucoid carcinoma shows secretion of mucus in small or large amounts by the cancerous epithelium. Scanty secretion of mucus may be seen only microscopically, in the form of signet ring cells each containing

- (b) Extra ductal or infiltrative-adenocarcinoma spheroidal cell carcinoma. and diffuse anaplastic types of carcinoma
- (c) Metaplastic types of growth-mucoid ('colloid') carcinoma, including signet ring-cell carcinoma and squamous cell carcinoma

(a) Intra ductal types of growth

Cheatle's important studies of pre invasive carcinoma, still confined within duct boundaries are readily verifiable by any student of breast pathology. The duct epithelium for short or long distances shows carcinomatous change in situ. and the duct lumina become filled and distended by the proliferating cancerous epithelium. The patterns assumed by this intra ductal growth vary (Figs. 67.73)



Fig. 71 -Intra ductal caremoma in an area of cystic hyperplasia (x 60)

They include papillary carcinoma, not sharply separable from simple papilloma cribiform or laciform carcinoma and solid masses of cells completely occluding the distended ducts. All of these forms of growth may be seen in one breast, and of course may coexist with areas of invasive carcinoma. The so-called comedo carcinoma consists of such intra ductal growths which along with products of degeneration or secretion in the obstructed ducts are expressible from the cut surface of the tumour Clearly the prognosis of tumours which consist wholly or largely of growth still confined within duct boundaries is much better than that of tumours of predominantly invasive types. But before pro-

nouncing favourably on such cases the pathologist must examine many parts of the discused breast in search for invasive growth for it is the presence or absence of this which will determine the prognosis

(b) Extra ductal infiltrative carcinoma

Invasive tumours may develop by escape of previously intra ductal growths from their duct confines or may arise ab initio from duct or alreolar epithelium Their structure is protean and variants of all types frequently occur in one tumour

(a) Spread in the ducts

What appears to be spread of growth within the duets of the breast results, I believe, almost always, not from invasive extension, but from spread of the cancerous change in the duet epithelium. Appearances clearly attributable to invasion of a duet by investing tumour cells are occasionally seen, but the occupation of long reaches of duets or of many small duets by intra duetal tumour, as in Figs 67-73, is due to origin of the tumour in situ and not to permeative growth

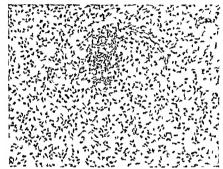


Fig. 76 -From a lymph nodal metastasis of signet ring-cell carcinoma of breast (x 120)

(b) Lymphatic oedema of the skin

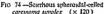
Nelation is credited with having first used the apt term 'peau d orange", and Banks (1900) applied the name, 'pig skin" to the same condition In 1909 Leitch showed that this was a thickening of the corium due to cancerous occlusion of the deep dermal lymph vessels the pits in the swollen skin being the exaggerated orifices of hair follicles. While most subsequent writers have agreed with Leitch that continuous permeation of the lymphatics by tumour cells was the essential lesion in peau d orange, Haagensen and Stout pointed out that embolic extension rather than continuous permeation in the dermal lymphatics probably plays an important part in the early stages. Since pig skin denotes more or less extensive spread by lymphatic channels, it is a bad prognostic sign even when of limited extent, when a considerable fraction of the skin of the breast is affected surgery is never curative.

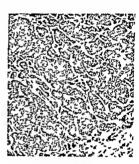
(c) Satellite nodules and cancer en currasse

These are late results of embolic and permeational spread in the dermal and deeper lymph vessels Extending occlusion of these vessels by growth leads to an extending zone in which embolic dissemination in lymphatics of small calibre is constantly taking place in a centrifugal direction. Each arrested embolic setablishes a new focus of growth from which further permeation and dissemination.

a globule of mucin these may be few in number and mingled with ordinary spheroidal cell growth, or they may outnumber other cells and give parts of the tumour a slightly translucent gelatinous appearance (Fig. 76). When abundant mucius is secretud, this is dischirged extra cellularly in large amounts, and typically gelatinous or "colloid cancers result. It has often been stated that these are relatively favourable in prognosis but this has not been my experience although some of these tumours grow rather slowly in the breast, they are no less productive of metastases than other invasive types of growth. Cheatle and Curler also in a thorough study of 10 cases of gelatinous cancer failed to substantiate their supposedly low malignancy. Calcification sometimes occurs in the more chronic gelatinous carcinomas as in the case reported by Shore







F10 75 - Cellular spheroidal-celled euremoma simplex (\$\times 60\$)

(ii) Squamous metaplasa — Squamous metaplasa is rater in mammary care nomas than might be expected in view of the development of the breast from the ectoderm. I saw it in only 5 of 552 surgically treated cases (Figs. 77 and 78). It is usually present only in parts of the tumours and is of no special prognostic import. Foot and Moore saw an epidermoid carcinoma of the breast with wide spread metastases which also showed squamous cell structure. I have examined a breast containing a spheroidal cell carcinoma and showing simple squamous metaplasia in ducts elsewhere.

(11) The direct spread of mammary carcinoma

I propose to say little on this subject for the routes of spread have been discussed in Chapter 9 and the details of local spread of breast cancer are of far less importance than its powers of metastasis. Certain special points only deserve comment here.

Others have shown no special skin lesions, but the tumours have grown rapidly and diffusely in the breast, and have been accompanied by oedema, redness and heat, and sometimes by pain and tenderness. This condition, especially if occurring during pregnancy or lactation, may be mistaken for acute mastitis or abscess, as in Case 332 of my 1941 paper. Taylor and Meltzer have given a good account of "inflammatory" carcinoma.

(12) The metastasis of mammary carcinoma

Metastases from carcinomas of the breast occur frequently and in many and diverse sites. In 45 consecutive necropsies (Willis, 1941), I found metastatic growths in the following situations

| Lymph gla Pleura Peritoneur Pericardiu Remote n | n m | - - - - / bloo | - - - d bo | - | 36 c 19 6 2 | cases | (80 per cent) | Thyroid gland Dura mater Brain Kidneys - Spleen - | 1111 | 8 cases 7 7 7 4 |
|---|--------|----------------------------|---------------------|---|----------------------|-------|---------------|---|------|-----------------------------|
| metasta | ses pi | resent | ın | _ | 33 | | (73 per cent) | Intestinal muco | 333 | 4 |
| Lungs | - ^ | - | | _ | 28 | | (6t per cent) | Pancreas - | - | 3 |
| Liver | - | - | _ | - | 22 | , | (49 per cent) | Ovaries - | - | 3 |
| Bones | *** | - | - | _ | 21 | • | (47 per cent) | Myocardium | - | 2 |
| Adrenals | _ | - | _ | - | 9 | , | | Endometrium | - | 1 |

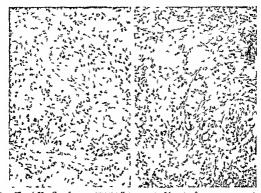
Of course these figures apply to the final stages of the disease. The frequency of metastases in particular sites in earlier stages is difficult to determine, but that they are often present is shown by the disappointing frequency with which, following successful removal of the breast in cases adjudged operable, metastatic growths in various situ tions subsequently manifest themselves.

(a) Metastases in regional lymph glands

The commonest site of secondary growths from mammary carcinoma is in the axillary group of lymph glands and these growths are established by embolism, not by continuous permeation (see Chapter 10). The frequency of axillary deposits in amputated specimens necessarily varies from series to series according to the enteria of operability adopted. In 622 radical mistectomies with microscopic examination of the axillary glands, Haagensen and Stout found these involved in 385. The 62 per cent. My own experience is in close agreement with this, 280 radical mistectomies I found axillary deposits in 158. To 56 per cent. Dawson (1943) found axillary involvement in 70 per cent of operation cases. As might be expected, the frequency of axillary metastases is related to the known duration of the tumours prior to operation. Thus in Haagensen and Stout's series, axillary deposits were present in 50 per cent of cases of duration between one and six months and in 68 per cent of cases of more than six months' duration. As noted above, about 80 per cent of fatal cases show axillary deposits.

Of all the factors influencing post operative prognosis, the condition of the axillary glands is the most important. Thus in the series reviewed by Lane Claypon 66 per cent of cases with unaffected glands survived for 5 years and 57 per cent for 10 years but when the glands were diseased the percentages were

proceed Satellite nodules in skin and fasciae are local embolic metastases, which however soon become confluent with one another. In cancer en cuirasse, the spread is more diffuse and affects all available tissue interstices as well as lymphatic channels.



Figs. 77 and 78 —Cornifying squamous-cell carcinoma of breast—from primary growth and axillary metastases (\times 60)

Typical cases of widely disseminated skin nodules were carefully studied by Handley (1922) who also reviewed some earlier records. Carnett and Howell saw unusually widespread nodules over the entire trunk, on the limbs face and scalp and also in the oral mucosa and vaginal and rectal walls. In cases described by Richl and by Goldsmith seirthous plaques in the scalp were accompanied by loss of hair. Askanazy and Jentzer saw cases in which dermal nodules caused pain and local sensory disturbances, due to close investment of cutaneous nerves by the growths. Newcomb saw deep pigmentation associated with skin nodules, due to vascular proliferation and haemorrhages in and beneath the endermis

(d) Telangiectatic or erysipelatoid carcinoma

This is a form of mammary caremonia which besides involving the dermal lymphatics, extensively permeates and disseminates in the small blood vessels of the skin and other tissues. The nodular hyperaemic areas are not necessarily restricted to the neighbourhood of the breast but may develop also in other parts of the trunk neck or face doubtless from metastatic foci. For good accounts of this condition see Weber and Dawson and Shaw

(e) Inflammatory carcinoma*

Some of the cases so designated have been of the 'erysipelatoid' type

practice would certainly obviate many useless operations. In many eases, however, remote metastases will clude even the most thorough clinical search and will not make their presence evident until months or years—even 15 or 20 years—have clapsed

Secondary tumours in the lungs, present in nearly two thirds of fatal cases, appear usually as scattered discrete well defined growths, less often in the form of miliary careinomas or of nodular lymph-vessel eareinosis of the lung and visceral pleura. Of course, direct invasion of the parietal pleura from the primary growth or from affected supraclavioular or mediastinal lymph glands may lead to transpleural involvement of the lung or to intrapleural dissemination and effusion.

Secondary tumours in the liver, present in about one half of fatal cases, are nearly always well defined discrete growths, rarely diffuse infiltrations (references Willis, 1934, p 253) The tumours show no particular distribution in the organ but are scattered indiscriminately in all parts. They clearly reach the liver bythe blood stream, and not by epigastric lymphatic channels as suggested by Handley

Secondar) tumours in bones are present in about one half of fatal cases (47 per cent in my series, 52 per cent in Kaufmann's). Contrary to Handley's contention, their distribution does not show any centrifugal relationship to the primary growth, like other metastatic tumours in bones they occur most frequently in those bones which contain abundant red marrow, and most of them are clearly blood borne deposits in this tissue (Willis, 1934, p. 332 and 337-342). Their usual effect on the bone is osteolysis, but dense osteoplastic change is not uncommon. Extensive metastases may be present in bones which appear radio graphically normal (Willis, Haagensen and Stout). Metastases in bones may produce the first symptoms of the disease (references, Willis 1934, p. 198, and Trinea and Willis, Case XVI), or they may manifest themselves many years after removal of the primary tumour (Willis, p. 112).

Secondary tumours in the brain are present in about 20 per cent of fatal cases of manimary carcinoma and the most frequent source of metrstrute growths in the brain is cancer of the breast. These are usually discrete well defined growths, often multiple, and situated in any part of the brain. Multiple metastases in other organs are present in most cases but a solitary metastasis may be found in the brain only (Willis, 1939). The following case is remarkable for the long period—nearly 15 years—intervening between apparently successful removal of the primary growth and the appearance of symptoms due to cerebral metastases and for the presence of massive calculation in these

Care XIII —A woman aged 52 was admuted to hospital in December 1934 under the diagnosis cortextal lumour or abscess. She had had ataxia failure of vision headaches and vomiting for 3 months and early papilloederia was present. Examination also showed the healthy scar of previous radical removal of the left breast performed early in 1920. Ventriculography revealed a large filling defect of the left ventricle corresponding to which there was a large area of heavy calcification in the posterior partial region. Operation (Mr H C Tumible) disclosed a well defined partly cystic partly calcified tumour 7 centimetres in diameter. This was removed. Microscopical examination showed spheroidal-cell carcinoma with widespread necrosis and calcification. The patient died 1 week after the operation. *Mecrops*, revealed lumour deposits in the hidar regions of both lumps and in the mediasinal lymph glands some residual tumour tissue in the operation area of the brain a metastasis 3 centimeters in diameter in the

only 29 and 14 respectively So also Haagensen and Stout found that when the axilla was clear of disease, the percentage of 5 year clinical cures was 61, but that when axilfary metastases were present, it was only 21 per cent

Careful dissection and microscopic examination are essential to determine the presence or absence of early arillary metastases, clinically impalpable glands may contain metastases and enlarged glands may contain none. Thus in Haagensen and Stout's series microscopical study revealed tumour deposits in 44 per cent of cases in which the clinician believed the glands to be unaffected while no tumour deposits were found microscopically in 15 per cent of cases in which the clinician had believed them to be present. Haagensen and Stout mention a case in which massively enlarged glands measuring up to 3 centimetres in diameter contained no growth and I have seen similar cases. However, glands 2.5 centimetres or more in diameter arearly found clear of tumour

Axillary tumours may attract attention long before any abnormality is apparent in the breast. References to such eases are given in my 1934 work (p. 197) and the following are additional examples.

Case XY—A woman aged 52 had noticed an enlarging mass in her right stuffa for 2 months. No abnormality of the breast could be detected. The enlarged axillary glands were existed, and were found to be massively replaced by active spheroidal-cell carcinoma. The largest gland measured 6 centimetres in diameter. Radical removal of the seemingly normal breast was performed there was no growth in the main part of the organ but in the axillary tail close to several remaining cancerous lymph glands there was a small primary carcinoma 12 centimeters in diameter.

Case XII—A woman aged 47 had noticed an enlarging mass in the right axills for months. It was excised and found microscopically to be a greatly enlarged lymph gland replaced by glandular and spheroidal-ceil carcinoma. Careful re-examination of the breast then detected very slight pean d orange above and lateral to the hipple but without any palpable tumour the breast was removed. Naked-eye examination disclosed no obvious tumour in any part of the organ which however especially its outer half showed generalized finely nodular thickening. Microscopical study of the implied area and the lateral parts of the breast showed mild hyperplastic changes with some dilated duets and microscopic areas of spheroidal-cell carcinoma infiltrating lymphatics.

Spread to the cervical, mediastinal or inguinal lymph glands often takes place in the later stages of mainimary carcinoma but rarely, if ever, precedes involvement of the axiliary glands. These more remote groups of glands become affected as the result of embolic or permeational spread from gland to gland or retrograde embolic dissemination following occlusion of the axiliary lymphatic paths (see Chapter 10). Halsted s operation for the removal of supraclavicular glands has lost favour patients with deposits in these glands should certainly be classed as inoperable.

(b) Metastasis by the blood stream

In the late stages of breast cancer remote metastases are of course frequent and often widespread as the list given above shows they are present in about three quarters of fatal cases. The lungs liver and bones are their commonest sites and the frequency with which such metastases develop following otherwise successful treatment of the primary growths fully justifies Hangensen and Stout is practice of including in their routine examination of every new patient skingrams of the lungs and of the entire skeleton except the distal parts of the limbs. This

controlled series of cases is necessary However, from the evidence so far, it seems clear that temporary retardation of growth has occurred in some oestra treated cases

It has long been recognized that carcinoma of the breast appearing during pregnancy or lactation is often highly malignant and speedily fatal. Dawson's study of 15 cases showed this to be due more to early dissemination than to unusual rapidity of growth of the tumours. These showed a range of structure and differentiation similar to that seen in carcinoma of the functionally quiescent organ, and only a few of them were highly anaplastic, but invasion of the lymphatics or blood vessels of the vascular active breast was often seen, and many of the patients soon died from metastases. However, the exacerbation of growth of some circinomas of the breast during pregnancy and lactation and their retardation following weaning (as in my Case No. 332, 1941) point plainly to hormonal factors controlling the rate of growth. Future researches in this field will include not only clinical studies but also hormone assays in suitable cases, and the experimental study of the fluctuations of growth of mammary tumours in animals as the result of pregnancy and of the administration of hormones.

(14) Carcinoma of the male breast

Valuable descriptions and reviews include those of Speed, Wainwright, Cheatle and Cutler, Gilbert, and Scarff and Smith The disease occurs with a frequency of only about one hundredth that of caneer of the female breast age of affected males is about 54 years, ages ranging from 12 to 91 have been recorded Trauma has often been blamed, but is of very doubtful significance

Gilbert cited the recorded cases in which maintary hyperplasia (gynaeco mastia) co existed with carcinoma of the male breast an association which was present in 9 of 47 cases in his own series. Villeon (cited by Gilbert) and Burrows have recorded cases of maintary cancer associated with prostatic enlargement. These clinical observations along with the experimental production of carcinoma of the breast in male mice by oestrogens (Chapter 4), strongly suggest that hormonal disturbance is a causative factor in this disease.

Pathology

In structure growth metastasis and prognosis, cancer of the breast in males closely resembles that in females The site of origin of the tumour is seldom far from the nipple, and as might be expected, both ulceration of the skin and invasion of the subjacent muscle and chest wall often occur sooner than in the female breast Paget's disease is rare. In more than half of the cases, the axillary lymph glands are already affected when the patient first comes under observation and operability and prognosis are often unfavourable. The commonest sites of remote metastases are lungs, liver and bones.

The two following personally studied cases are notable the one because the tumour was in an early stage and still confined within the ducts the other because

it was of the rare intra cystic papillary type

Case XVI (Dr Norman Freemantle's case)—A man aged 72 had a blood stained discharge from his nipple and then felt a small mass in the breast. No axillary glands were palpable local mastectomy was performed. The thickened tissues beneath the

middle of the cerebellum, and a metastasis I continuence in diameter in the white matter of the right frontal lobe. There were no metastases in any other organs and no sign of recurrent growth in the mammary area. Sections of the original breast tumour were available and comparison of these with sections of the cerebral and mediastinal growths left no doubt that these were indeed metastases of the former.

Secondary tumours in other parts. Accounts of these are given in Part II of my 1934 work, and elsewhere also I have described metastises from carcinomas of the breast in the throat gland (1931), and in the intestines (1931). The following case showed clinically prominent splenic and other metastases from an inconspicuous primary growth. (For references to other cases of diffuse metastalic carcinoma of the spleen see my 1934 work. p. 287.)

Case AIV — A woman 61 years old complained of avaerina and weakness of 10 months duration and of intermittent diplopia Examination showed marked pallor one enlarged cervical lymph glands and palpably enlarged spleen and liver Both breasts were somewhat nodular to palpation but no definite growth was detected. Test meal showed total achiohydrian but no lesson was usable in skingarms following barum meal or barum enema. Diagnosis of primary anaemia was made, but section of a gland remoted from the neck showed secondary spheroidal-cell carenioma. Necropsy revealed an ill defined area of induration in the right breast which proved microscopically to be a diffusely inflittating spheroidal-cell carenioma. The liver was enlarged and studded with secondary growths. The spleen 820 grammes was uniformly enlarged and hard its cut surface showed ill defined diffuse and confluent patches of white growth resymbling the porphyry spleen of Hodgkin's disease microscopically it showed widespread carranomatious infilitation. Both adrenals were enlarged by metastatic growths. The inner aspect of the censual dura mater was studded with many projecting nodules and flat plaques of turnour. Section of the bones was unfortunately ornitted. Other organs were normal.

The following case is notable in showing multiple metastases in uterine myomas, as seen also by Schmorl

Care VI —A woman aged 50 with recurrent carenoma of the breast had had some recent uterine haemorrhage but no growth was found in curetings microscopically Necropy disclosed metisfases in lungs liver kidness adrenals bones thyroid gland ovaries and uterin, myomas The uterus contained about 14 myomas, the 2 larget of which in the fundus were each 4 centimeters in diameter 1 intranural and 1 submucous These 2 contained about 16 myomas showed a small focus of carenoma. Sections of 8 of the smaller myomas showed a small focus of carenoma it only. The normal myometrium and the endowntum were clear of exosts.

(13) Harmonal factors influencing the growth of mammary carcinoma

Two seemingly opposed observations on the hormonal control of breast cancer have been made. On the one hand, during the last fifty years there have appeared repetited claims that removal of the owners or suppression of ovarran function by X ray stradation retards the growth of some carcinomis (Beatson Lett Taylor). On the other hand there are recent claims that the administration of oestrogens is beneficial in some cases of the disease (see for example Haddow et al.). Final judgement of the validity of both these claims must be defurred. Whatever beneficial effect loss of ovariant function may have it must certainly be only relative or temporary since many carcinomas of the breast develop and grow actively long after the menoptuse. As regards the possible benefits of oestrogen therapy many of the favourible claims have been based on single or few cases and the periods of observation have been brief. In their study of large

I have seen in these cases nothing peculiar nothing which might not be written in the ordinary history of cancer of the breast I believe that a nearly similar sequence of events may be observed in other parts. I have seen a persistent rawness of the glans penis, like a long enduring balantits, followed after more than a year s duration by cancer of the substance of the glans." Paget explained the minimizing cancer as a result of the surface lesion "it may be suggested that a superficial disease induces in the structures beneath it, in the course of many months, such degeneracy as makes them apt to become the seats of cancer."

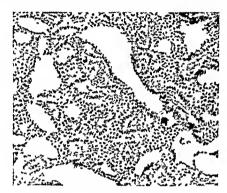


Fig. 81 -Case VIII Intra ductal carcinoma of male breast (× 120)

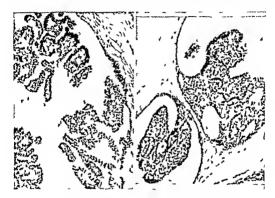
(2) Diverse views on histogenesis

While Paget believed the disease of the nipple to precede the development of cancer in the breast, many later workers took the opposite view that the surface lesion was secondary to an already established intra mammary growth. It is unnecessary to review this controversy in detail. Histological studies have now made it clear that, in those frequent cases in which Paget's disease coexists with a deep seated invasive mammary careanoma, the former is not due to invasion of the nipple from the latter. In many cases there is no anatomical connexion between the two lesions (e.g. Case XX below) and, in some cases of Paget's disease (e.g. Cheatle and Cutler's Case 6 and my Cases XVIII and XIX below), there is no associated invasive mammary growth. Paget's disease is thus primary in the nipple region itself and the frequently coexisting carcinoma of the breast is an independent primary growth.

Microscopical examination shows that in almost all cases of Paget's disease the epithelium of one or more main ducts within the nipple has undergone carcino matous change (Figs 91 92) Often this growth is still confined to the ducts and has not produced any mass of tumour obvious to the naked eye. In most

nipple contained formous dilated ducts with brownish contents and formed an ill-defined mass 2 centimetres in diameter, and microscopical examination showed that the epithelium liming the cystic ducts was caranomatous but still within the duct confines

Case XVII—A man aged 58 had had an en'arging lump in the breast for 2 years local mastectomy was performed. The breast contained an irregularly loculated cavity 4 centimetres in diameter tightly distincted by blood standed fined and a mass of fruible growth. Microscopical examination showed this to consist purity of well differentiated finely papillar growth and partly of more solid irregular papillary carcinoma springing from many parts of the evist and shited ducts and still confined within them (Figs. 79-81)



Firs 79 and 80 -Case XVII Intra ductal carcinoma of male breast (x 120)

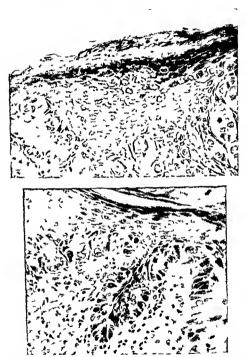
PAGET'S DISEASE OF THE NIPPLE

For excellent descriptions of this disease and discussions of the various views as to its histogenesis see Cheatle (1923) Cheatle and Cuiler Muir (1935 and 1939), and Inglis (1936 and 1940)

(1) Paget's original description

Paget's account in 1874 of the clinical characters of 15 cases of the disease has not been bettered and the following passages from his paper are particularly noteworthy. It has happened that in every case which I have been able to watch cancer of the mammary gland has followed within at the most two years and usually within one year. The formation of cancer has not in any case taken place first in the diseased part of the skin. It has always been in the substance of the mammary gland beneath or not far from the diseased skin, and always with a clear interval of apparently healthy tissue. In the cancers themselves,

to changes in the epidermal cells in situ and Paget's disease being due to intra epidermal spread of cancer"



Figs 83 and 84—Case XVIII Paget's disease Fig 83 shows that some of the Paget cells are cells of the stratum granulosum and contain eledin granules Fig 84 shows a part where all the cells of the basal layer have undergone Paget change (× 300)

From my own study of 6 cases of Paget's disease and of the records of others, I am satisfied that it is a form of epidermal carcinoma m situ I agree with Arnd and with Cheatle and Cutler that transitions between epidermal and Paget cells

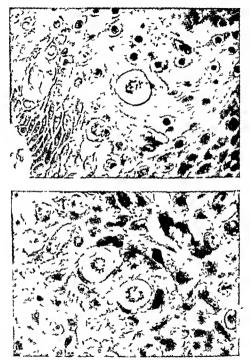
cases the neoplastic change in the ducts extends right up to their exits on the nipple, so that the cancerous duct epithelium and the epidermis affected by the Paget s disease are in continuity. On the other hand in cases in which an invasive caremoma is present deep in the breast this growth may or may not be in continuity with the caremomatous duct epithelium in the nipple



Fig. 82 -- Case XVIII Paget's disease a general view (× 96)

But there are still two conflicting views regarding the histogenesis of Paget's disease—(a) that it arises as a primary carcinoma of the epithelium of the main ducts in the nupple and that the surface lesson results from intra epidermal spread of the carcinoma cells (Mur., Ingles) and (b) that it is a primary epidermal change—carcinomatous or pre-carcinomatous—and that the neoplastic change in the duct epithelium is concomitant (Cheatle and Cuthr.) My own studies consince me that the second view is the correct one

The problem of histogenesis centres around the identity of the Paget' cells which were discovered in 1889 by Darier, who at first believed them to be parasitio psorosperms' These are large pale rounded or polyhedral cells present, singly or in small or large clumps in the affected epidermis and often containing mitotic figures. These cells are present in all true cases of Paget's disease (Figs Are they invaders from the neighbouring neoplastic duct enthelium or are they cancerous or pre-cancerous cells of the epidermis itself? Arnd showed by Best's method that the Paget cells were rich in glycogen and that transitions between normal emdermal and the glycogen rich cells could be demonstrated and he accordingly likened Paget's disease to Bowen's "pre-cancerous derma tosis' So also Cheatle and Cutler concluded that 'Paget's cells can be traced developing from epidermic cells in all stages of formation ' an opinion endorsed also by Ludford from a close extological study of some of their material. Inches on the contrary could discover no transitions between epidermal cells and Paget cells and therefore concluded that Bowen s and other pre-cancerous dermatoses and Paget's disease are "fundamentally different Bowen's disease being due of the special situation of the disease The almost regularly coexisting neoplastic change in the ducts does not prove a duct origin for the Paget's disease, con-



Figs 87 and 88 -Case YIX Pagets disease showing Paget cells in mitosis (x 500)

comitant change in a field of tissue including both ducts and epidermis is an equally (I think, more) plausible explanation. And finally there occur cases like Cheatle and Cutler's Case 6 in which Paget's disease is not accompanied by neoplasia in the upper reaches of the ducts.

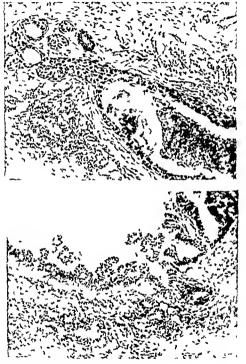
are to be seen. Occasionally, indeed cells which are unmistability epidermale g cells situated in the granular layer and containing keratohyalin granules or



Figs 85 and 86—Case VIV Pagets disease Fig 85 shows the characteristic cells some in mitosis. Fig 86 shows cells of the stratum granulosum with early Paget changes. (× 300)

swollen spinous cells—are also Prget cells (Figs 83 and 86) Microscopical differences between Paget's disease and Bowen's disease do not warrant the conclusion that they are 'fundamentally different', the cytological peculianties of Paget's disease especially the plentiful Paget cells, may be expressions only

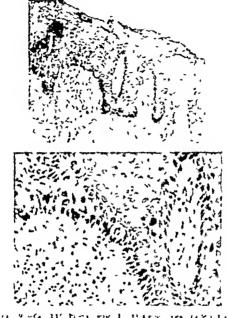
had not produced any tumour obvious to the naked eye. Deeper parts of the breast contained no growth. The enlarged axillary glands showed irritative hyperplasia only



Figs 91 and 92—Case YYI Paget's disease Two views of the intra ductal carcinoma in the nipple region (x 120)

Case XIX—A woman aged 60 had noticed "inflammation" of the nipple and arola flattening of the nipple for 2 years | Examination showed a circular area of Paget's disease 3 centimetres in diameter but no patigable tumour in the breast | mastertomy

(3) Personalir studied examples of Paget's disease Of my 6 case, the following exemplify many of the characters of the disease



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MUIR R (1941) The evolution of carcinoma of the mamma J Path Bact 42 155 (Important studies of Paget's disease and of the mode of origin of mammary careinoma) was performed Microscopy-Typical Paget changes in the epidermis (Figs 85-88) accompanied by intra duct carcinoma in the nipple area, but no invasive growth in the breast

Case XX -- A woman aged 41 had noticed a discharge from the nipple for 12 months and a mass in the breast for 2 months Radical mastectomy was performed epidermis of the nipple and arcola was red and scaly and showed the typical microscopical changes of Paget's disease. The ducts in and immediately beneath the nipple were dilated and showed intra-duct carcinoma without any invasion of surrounding tissues and without any turnefaction visible to the naked eye. One part of the periphery of the breast contained an area of invasive carcinoma 2 centimetres in diameter accompanied by intra duct careinoma in some dilated ducts adjacent to it. The tissues intervening between this area of growth and the diseased nipple appeared clear of tumour for a distance of at least 3.5 centimetres and this was verified in several micro sections. Other parts of the breast showed some general fibrosis and dilatation of ducts but without tumour. The axillary lymph glands were clear of growth

Case XXI -A woman aged 39 had had 'eczema of the right nipple for 18 months commencing 4 months before the birth of a child and extending slowly during 9 months lactation and after Examination showed a circular red area 4 centimetres in diameter with the retracted nipple at its centre a large irregular mass in the breast deep to the nipple extending both medially and laterally especially into the axillary tail and a firm mass in the axilia. The amputated breast contained an irregularly pyramidal mass of growth with its apex at the nipple Microscopically the epidermis showed typical Paget s disease (Figs 89 and 90) The breast showed widespread intra-duct and invasive carcinoma supervening on cystic hyperplasia the invasive growth was situated mainly in the perioheral parts of the mass, while in the nipple region the growth was still mainly within the ducts (Figs 91 and 92)

Cases XVIII and XIX exemplify Paget's disease accompanied by intra duct carcinoma in the nipple but no invasive growth in the breast. Case XX. Paget s disease with intra duct carcinoma in the nipple and a separate focus of invasive carcinoma in the breast, and Case XXI, Paget's disease intra duct carcinoma and invasive carcinoma all continuous

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CHAPTER 14

EPITHELIAL TUMOURS OF THE SKIN

Skin tumours are of special interest for several reasons. They can be observed from their inception, they are often removed in early stages so that their mode of origin is readily studied, and much is known about their causation. The skin was naturally enough, the first tissue in which occupational tumours were recognized, and this recognition led to the experimental production of tumours and to the discovery of chemical carcinogens (Chapter 4). An important fact to remember in statistical studies of skin cancer is that, although its clinical diagnoss is fairly reliable in civilized countries, mortality statistics are of no value for making comprisions of its incidence in different communities or for estimating trends, this is because of the high cure rate with modern methods of treatment

CAUSATIVE FACTORS AND PRE CANCEROUS LESIONS

For valuable outlines and reviews of this subject, see Hueper, Mackee and Cipollaro, Haagensen, and other references given in Chapter 4

(1) Age incidence

Because of the diversity of known causative factors and the different periods of life at which they operate, little is to be gained by a close analysis of the age incidence of skin cancer in general Some tumours, e.g. those in cases of xeroderma pigmentosum, some X-ray and radium cancers due to therapeutic applications have developed in youth, but most tumours due to sunlight tar, oils, various ulcers, osteomyelitis sinuses, or old scars, and most of those of uncertain causation have appeared in middle or old age. Age distribution curves while showing cases of skin cancer scattered through the earlier decades, rise steadily during the fourth decade and show a rather blunt summit not a sharp peak in the fifth sixth and seventh decades With many of the later appearing skin tumours of known causation, the interval between application of the responsible agent and appearance of the tumour is a very long one-10, 20 40 years or longer Hueper gives references to many examples of long induction period. In some series e g Savatard s the average age of appearance of basal cell growths has been less than that of squamous cell growths In most series however, the reverse has obtained, thus Treves and Pack found the mean ages of patients with squamous cell and basal cell caremomas to be 58 and 61 respectively and Shrek and Gates found the commonest age of onset of the two types to be 57 and 66 respectively

(2) Sex incidence

Skin cancers as a whole, and almost all of their distinct occupational varieties, occur more commonly in men than in women. Some occupational turnours (e.g. in cotton spinners chimney-sweeps arsenic workers and radiologists) are almost restricted to males. Actine cancers predominate in males, so also do

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xeroderma pigmentosum are really actinic cancers, the skin having an inherited super sensitiveness to light Copeland and Martin give a good account of xeroderma pigmentosum, and Mathews discusses photosensitization in relation to actinic carcinomas. The commonest sites of skin cancers in outdoor workers are the face and neck and the dorsa of the hands and forearms. Actinic cancers may be of either the squamous-cell or basal cell type, and multiple tumours some of one type and some of the other, are frequent. They are commonest in the sixth and seventh decades.

(d) X-ray and radium cancers

X ray and radium cancers, always of the squamous cell type, may be due to either occupational or therapeutic exposure. The occupational tumours, now less frequent than in the early days of radiology, occurred usually in men, in the fourth or fifth decade, most commonly on the hands and forearms, and they were frequently multiple. Tumours resulting from therapeutic exposure of course show a less regular age, sex and site incidence. Haagensen recorded 5 examples of carcinoma from therapeutic X ray irradiation, and Hueper gues other references. I have seen several examples of carcinoma arising in areas where other lesions had previously been treated by radium. The most trage of these was in a youth of 18, who for 18 months suffered from a deeply invasive ulcerated squamous cell carcinoma of the neck which arose in a sear resulting from application of a radium pack to a skin tumour when he was 3 years old

(e) Carcinoma af scars (Marjolin's ulcer)

Carcinomatous change has been observed in the scars of burns, of lupus vilgaris, of lupus erythematosus and of wounds Usually the tumours appear many years after the infliction of the injury, sometimes as long as 30 or 40 years, but in elderly people with already keratotic skins, a burn or other injury may be followed promptly by a tumour. Treves and Pack therefore properly distinguished between acute burn cancers supervening within a few months of the burns, and cancers of old burn scars in which the average induction period in their cases was 32.5 years. Scar cancers are usually of the squamous cell type but basal cell growths also occur. Treves and Pack's cases comprised 21 epider and and probabal cell carcinomas, the latter usually in cases in which hashible as and be superficial, sparing hair follicles and sweat glands. Haagens or longer to the scar instances of basal cell carcinoma at the sites of small burns of the scar cancers following lupus vulgaris of lupus erry the following intradiation has been blamed, but cancer has appeared also in place for the following fatal scar carcinoma following total avulsion of the scalp 21 years following in a scar is often multifocal or widespreakes. Projected a remain following total avulsion of the scalp 21 years following in a scar is often multifocal or widespreakes. Projected accordingly (Willis, 1945)

(f) Carcinomas af varicase ulcers

These occur about equally in men and women most commonly in the fifth sixth and seventh decades, are always squamous celled, and may be multiple or of widespread origin (see Figs 6 and 7)

those arising in sears in osteomyclitis sinuses and in arsenical dermatitis resulting from therapeutic administration of the poison. Careinoma arising in viricose ulcers affects men and women about equally. Sub-epidermal growths both those of basal-cell type and those of glandular type are commoner in women than in men.

(3) Recognized factors in causation

(a) Carcinogenic hydrocarbons

Careinogenic hydrocarbons are responsible for pitch tar, ercosote oil paralin and chimney sweep's cancers. These are almost restricted to make appear most frequently in the sixth decade, and are always of the squamous-cell type. Pitch and tar cancers occur most commonly on the head neck foreign hand ascrotum oil cancers (notably mule-spinner's cancer) on the scrotum furcism and hand and chimney sweep's cancer (now in rise dwesse) on the scrotum Multiple tumours are common a good example is the patient described by O Donovan a mineral oil worker who had had 15 tumours removed and who had others developing on his nose car arms foreigns, grouns thigh and leg It is probable that the kangri cancers common on the abdominal will or thigh in kashmir natives (Neve, Vaughan) are due, not solely to the chronic burns from the kangri or charcoal heater, but to careinogenie ngents in the associated soot or tarry products

(b) Arsemcal cancers

Arsenical keratoses are prone to become earcinomatous. These lesions develop either in men engaged in occupations exposing them to arsenic or in patients of either sex who have taken arsenic medicinally, usually as I owler a solution for long periods. The tumours are commonest on the limbs less common on the face and rare on the trunk, and they are usually multiple and often numerous. Both squamous-cell and basal-cell growths occur in bout one third of them are basal-celled. (I or further details see I ranseen and Taylor)

(c) Actinic cancers

The careinogenic properties of sunlight and ultra violet light, now fully proved experimentally were long suspected by dermatologists who noticed the disproprionate frequency of keratoses and of basal-cell and squinnois-cell careinomis of exposed parts of the skin as compared with covered parts in outdoor as compared with motor workers in fair skinned people as compared with dirk-skinned people and in sunny as compared with cloudy countries (Molesworth Harpensen Phillips). Cancers of the skin in sailors fishermen farmers and pardeners are largely due to ultra violet radiation—and the most susceptible subjects are those with fair freekled skin which sunburns exist. As Molesworth misted sun bathing is dangerous for people of this complexion. I too have seen several case, of multiple careinomas of the skin in unusual situations in inseterate sun bathers (e.g. Case III below). Sunlight probably plays a major part in induring many semile keratoises and skin tumours of unidentified causation. Doubtless other careinoenia factors co-operate with sunlight. There is every reason to believe that the multiple skin cancers which arise at an entry age in ever of

be considered as a possible factor in the causation of skin tumours. This possibility, first suggested, I believe, by Peacock at a meeting of the Pathological Society of Great. Britain at Aberdeen in 1946, appears particularly plausible in cases of multiple sub-epidermal basal cell growths of predominantly glandular origin, as in Brooke's disease or "turban tumours" (see below). The sebum and sweat of these patients must be searched for carcinogenic substances. Experimentalists also must trace the cutaneous excretion of carcinogens given by mouth or other routes. As Peacock suggested, the association of degenerated parasites (Demodex), obstructing the glandular orifices, with some basal cell skin tumours, may not be purely fortuitous, it may be that the obstruction causes local accumulation of carcinogens which are constantly being discharged in small amounts by the skin glands.

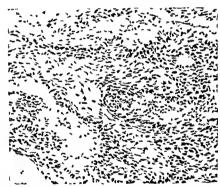


Fig 93 — Adamantinoma like structure in carcinoma of sebaceous cyst Case II (× 120)

(4) Sites of tumours of the skin

Clearly the site of a skin tumour will depend on which of the many and diverse causes just outlined are responsible. The main sites of the various causative groups of tumours have already been given briefly, and more will be said on this subject when discussing the several structural types of growths. Most large series of skin tumours record that 50 per cent or more of the tumours were situated on the face or neck. and since arseine, X ray irradiation or hydrocarbons can be blamed for relatively few of these this distribution points to the great importance of sunlight in causation. Facial skin cancers are more often multiple than others Phillips reported that of 1 400 patients with skin cancers in Texas, 226 had multiple tumours, varying from 2 to 23 in number, and except for 18 cases with fumours on the hands all of the multiple growths were on the face patients with multiple growths, 109 were farmers often fair skinned. Carcinoma of the conjunctiva, prevalent in horses and cattle (see below), is rare in main

(g) Carcinomas of osteomyelitis sinuses

Carcinomas of osteomychitis sinuses well reviewed by Bereston and Ney develop in chronic sinuses of long duration—usually 20 or 30, or even 50, years. They are most common in males between 40 and 60 years old and are always squamous-celled. The tibia is much the commonest bone affected. The tumours arise from the skin surface around the sinuses or from the partially epithelialized tracks and spread deeply into the diseased bone along the sinuses. Eliason and McLaughlin saw a man aged 34, with carcinoma of both legs arising in sinuses following compound fractures of both tibiae at the 19th of 6

(h) Carcinomas of other sinuses

Occasionally careinoma develops in other chronic skin sinuses The following is a probable example

Cate I(Mr. C. II. Hembrow's case)—Early in 1935 a woman aged 23 noticed a sore pumple or blind boil' near the middle of the gluteal creas. This dis harged some pus but failed to heal and it was incised or curricled 6 times during the ensuing 18 months in September 1936 the lesion appeared as an inflamed ramifying sinus extending deeply into the subcutaneous tissue. It was regarded as probably of developmental origin and analogous to a pilonical sinus—and the extensive tracks were widely exceed. Microscopical examination unexpectedly showed the tracks to be lined by a superficial layer of papillary endermoid careinoma. (Fig. 8)—The area remained healed for several weeks and then broke down again—and in spite of radiational treatment by November 1937—massive recurrent growth was present.

(1) Carcinomas of sebaceous cysts

These have been estimated to occur in from 3 to 9 per cent of such cysts but in view of the frequency of small cysts for which medical advice is never sought these are certainly over-estimates. Caylor s and Benecke s are good accounts of the subject. Most of the tumours are squamous-celled but some have been basil-celled and in Benecke's case the growth had a cystic glandular structure. The following is an illustrative case.

Case II (Mr. R. C. Brown a care) —A fair shanned farmer aged 60 with many facial terrators developed a rounded tumour of the temple which was diagnosed as a sebacrous cyst but which was accompanied by a small patch of warty growth in the overlying epidermis. The tumour excised along with an ellipse of skin proved to be a thick walled cyst containing a small amount of sebum. Microscopicilly the walls showed active squamous-cell carrinoms which had commenced to invade the overlying epid rmis and which showed administrational like structure in places (1 ig 93).

(1) Carcinoma following special skin diseases

This has been seen occasionally in association with lupus vulgaris lupus erythematoxus, psonaus or syphibs (Savatrid Flint and Gordon Hueper). In cases which had been treated by X-ray irradiation or by arsenic these agents have often been blamed for the supervention of the tumours but in other cases no such treatments had been used. Kraurosis and leucoplakin of the vulva are important pre-cancerous lesions (Chapter 12). Bowen's and other pre-cancerous derma toses—are really forms of intra-epidermal curenoma (see below).

(k) Exerction of carcinogenic substances

I scretion of executogenic substances by the sebaceous or sweat glands must

EPITHELIAL TUMOURS OF THE SKIN IN ANIMALS

Many references and illustrations are given in Feldman's book, Chapters 17 19



Fig. 95—Para anal tumour of Kolpie 14 years old—a well-defined good yellowish tumour 6 centimetris in diameter covered by intact skin (x 50)



Fig 96 -Tumour similar to that of Fig 95 from skin of chest of adult Airedale (× 60)

(1) Dogs

Dogs frequently develop epithelial tumours of the skin. These include epithemial papillomas especially of the ears adenomas of sebaceous, sweat of

Light is no doubt important also in the causation of timours of the hands and forearms, where, however, the occupational handling of carcinogenic agents must also operate. While tumours of the face ears, neck and hands are commoner in men than in women. Shrek found that the reverse applied to tumours of the scalp trunk and legs.

Taylor et al found that the sites of 430 epidermoid carcinomas of the limbs were—hand 284 leg 73 arm 41 feet 32. There was a history of some preexisting lesion in 193 cases (45 per cent), including sende keratoses in 63 arsenical keratoses in 14, injuries or scars in 36, burn sears in 23, radiation dermatitis in 10, osteomyelitis in 11 and varicose ulceration in 11.

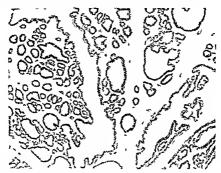


Fig. 94—Cystic adenoma of sweat glands of back of neck of a Pomeranian aged 6 growth was well defined lobulated of sponge like cystic structure the cystic containing clear watery fluid (× 80)

Excluding tumours resulting from X ray or radium butns and from known chemical agents currinormas of the fingers are rare. Sigel reviewed 22 recorded eases and the following two examples deserve mention

Case III (Mr C J O Brown s case) —A man of 54 for many years a sun bather on Victorian beaches developed 2 growths one on the dorsum of the wrist and the other on the side of a finger. These were cussed and sections showed squamous-cell carcinoms.

Case IV—For years, a man aged 67 had had gout with large tophi and for 18 months he had had an infected finger up. Examination showed a typical cartenoma dia amputation was performed. Microscopical examination confirmed the presence of an ulcerated squamous-cell cartenoma of the tip of the finger; and of a large gouty tophus surrounding the interphalangeal joint. There were no gouty deposits in the neighbourhood of the timour.

Epidermal carcinomas of the external genetalia will be described in Chapters 32 and 35

and are prone to recur following local removal Excision of the whole third eyelid is the proper treatment. The tumours grow slowly and for long remain superficial, but they eventually invade the eye or orbit. After the conjunctiva the pens, prepuce and vulva are the commonest sites of skin carcinoma, other sites are much less common.

(3) Cattle

Again the most frequent type of integumentary carcinoma is papillary squamous cell carcinoma of the conjunctiva But squamous cell cancer of the skin is also common, especially in blonde animals Drabble s study of skin cancer



Fig. 98—Basal-cell carcinoma of lower hp of adult fox terrier. Tumour, which slowly recurred after excision 2 years earlier, was 4 centimetres in main diameter, and irregularly lobulated with lobules almost discrete from one another. Note the racemose adenoid structure pointing to sweat glandular origin (7.50).

in cattle in Australia showed a striking preponderance of tumours in white or lightly pigmented areas of skin, and pointed strongly to sunlight as an important causative factor. Brand cancer" is of doubtful significance, its frequency has been falsely exaggerated, and factors other than the brand scar have been overlooked. Carcinoma of the base of the horn is said to be prevalent in India where loads are attached to cattle by the horns (references by Feldman) Squamous-cell carcinoma of the skin of the udder is more common than mammary carcinoma (Drabble).

(4) Sheep, swine and cats

Sheep and pigs only occasionally suffer from cutaneous or conjunctival squamous cell carcinomas, but it must be remembered that these animals are often slaughtered when young The rarity of skin cancer in cats, however, denotes

ceruminous glands (Fig. 94), invasive squamous cell carcinomas of the usual type liable to ulceration and metastasis well circumscribed sub-epidermal non metastasizing growths most frequently but not invariably from the peri anal area undoubtedly arising from the glands and consisting of rather characteristic columns and clumps of large polyhedral cells with only a slight tendency to cornify (Figs. 95. 96), and basal cell tumours of glandular or hair matrix origin, which grow in adenoid or reticular patterns (Figs. 97. 98). A prevalent idea that dogs have few or no sweat glands is false, sweat and apocrine glands are plentiful in dogs and are the principal source of their common basal celled and adenoid skin tumours. Nothing is yet known of the causation of skin tumours.

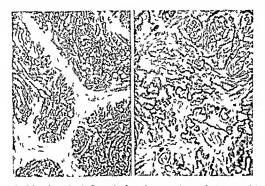


Fig. 97—Sub-epidermal basal-cell growth of reticular pattern from neck of a mongrel dog (A) shows lobular structure pointing to sweat glandular origin. (× 50 and 85)

in dogs. Their distribution—more often on hairy parts of the trunk and limbs than on bare parts of the face—shows that light is not an important factor—and their frequent origin from the glands suggests the possible action of carcinogenic substances excreted in sebum or sweat. The most frequent site of squamous cell carcinomas of the trunk is the skin of or close to the prepuce—and these juxta preputal tumours are sometimes multiple—Rudduck and I saw a male Alsatian aged 9 with a squamous cell carcinoma arising in the centre of the squatting callosity over the oleeranon—there were metastases in the axillary lymph glands

(2) Horses

Chronic papillary squamous cell carentoma of the conjunctiva is common, Rudduck and I studied 13 cases (Fig. 99) These turnours arise mainly in animals between 5 and 10 years old usually from the third cyclid they are often demon strably of diffuse origin over a considerable field of tissue are sometimes bilateral,

thickness, ridge pattern, stratification pattern, pigmentation, and depth of papillae, and at certain special regions, such as the muco cutaneous junctions, the evelids and conjunctiva, the external auditory meatus, the nipples, and the several parts of the external generalia, the epithelium has locally distinctive In spite of this structural diversity, however, the entire epidermis and its various appendages form a single system of closely allied components, all of which have developed from a common precursor, the foetal epidermis, and all of which in the adult show similar reactions in many pathological conditions including tumours. These tumours, like their parent epithelia, show great struc tural diversity, yet form a unified group in which, though we properly distinguish several main types, these are connected by growths of intermediate structure and No sharp distinction is possible between papilloma and carcinoma, between basal cell and squamous cell growths, between basal-cell carcinoma of the epidermis (rodent carcinoma) and sub epidermal basal cell growths arising from hair follicles or glands or between the latter and tumours of plainly glandular structure-adenomas or adenocarcinomas-of the dermal glands. Attempts to name and classify skin tumours on the assumption that each has arisen from either basal or spinous cells, or from either surface epidermis or hair follicles or sebaceous glands or sweat glands, have created artificial distinctions and a redundant terminology growths of similar structure may and do arise from any or all of these sites Hence, the following tabulation of the main structural variants of epithelial growths of the skin, while necessary and useful, does not imply any biologically sharp separations

(1) Papillonia (a) Squamous or horny and unpigmented (b) Pigmented

(2) Squamous-cell carcinoma

(3) Basal cell carcinoma (a) Superficial or rodent type

(b) Sub epidermal type

(c) Mixed basal and squamous cell carcinoma

(d) Basal cell carcinoma of the tibia

(4) Tumours of glandular structure arising from sebaceous glands

(5) Tumours of glandular structure arising from sweat glands

(6) Tumours of glandular structure arising from other special glands

(7) Intra epidernial carcinoma

(1) Papillomas of the epidermis

(a) Squamous or horny unpigmented papillomas

The commonest form is the cutaneous horn consisting of a localized sessile overgrowth of the epidermis surmounted by a short or tall conical mass of firmly attached keratin. Less usual are bulky cauliflower papillomas either sessile or pedunculated. Carcinomatous change occasionally supervenes in previously simple papillomas of long duration. Infective papillary overgrowths of the epidermis, such as warts or venereal condylomas, are not true tumours.

(b) Pigmented papillomas

Also called 'seborrhouse keratoses' 'senile warts', or "acanthotic naevi', these are common in the skin of middle aged and old people, as slowly growing sessile or pedunculated brown or grey firm masses with a finely nodular of

a real relative insusceptibility to this disease. Rudduck and I saw a basal celled adenoid tumour of the neck of an adult Persian cat

(5) Rodents

The spontaneous and experimentally induced epidermal tumours of nuce too well known to call for description. Rats, rabbits and guinea pigs are less susceptible, but it is of interest to note that actinic cancers are readily induced in rats (see Chapter 4), that these may be of either squamous cell or basal cell type and that Bullock and Curtis saw spontaneous basal cell as well as squamous-cell carenomas in rats.



Fig. 99 - Papillary carcinoma of third eyelid of horse aged 10 (x 60)

(6) Birds

Birds with skin tumours have seldom been described Emmel reported examples of epidermoid cancer of the feet of wild birds Rudduck and I saw a papilloma of the base of a claw in a magpie

(7) Lower vertebrates

The few records of tumours of the skin glands in amphibians, of papillomas in lizards and of carcinomas of the gill region in fish were mentioned in Chapter 6

THE VARIETIES OF EPITHELIAL TUMOURS OF THE SKIN

The integumentary epithelium shows great diversity of structure it includes the surface epidermis hairs and hair follucies nails sebuceous sweat and apoctme glands. The epidermis itself varies markedly in different parts of the body, in growths shows that the fields of origin of these are commonly areas of skin of not less than I or 2 centimetres diameter. The epidermis marginal to a young tumour often shows gradual hyperplastic thickening as it nears the tumour, and the hyperplastic epithelium is gently continuous with the neoplastic without any abrupt demarcation. The epithelium of the young tumour is often highly differ entiated and epidermis like, and its cancerous nature is revealed only by the invasion of the dermis. These features are exemplified in Figs. 2 to 5. Carcinomas arising in sears, ulcers or other extensive pre existing lesions are often demon strably widespread or multicentric in origin, the epithelium in the whole field of the pre cancerous lesion may become cancerous simultaneously or successively (Figs. 6 and 7).

(b) Microscopical structure

The familiar structure of well differentiated cornifying squamous cell or epidermoid careinoma is described and depicted in every text book, and is sufficiently illustrated in Figs 2 to 7 Epidermal careinomas show gradations between nearly epidermis like structure and diffuse anaplastic growth not recognizably epithelial. The following special structural features deserve comment

(1) Spinous cells—Spinous cells with plain intercellular bridges are often plentiful in well differentiated growths with cornified "cell nests" or "epithelial pearls", and are sometimes present in tumours in which cornification is not

conspicuous

(u) Spindle-sliaped cells—These are prominent in some tumours. Usually they are components of well defined epithelial masses but occasionally they occur in diffuse areas of growth and mimic "spindle cell sarcoma" in appearance (For a good account of spindle cell careinomas of the skin, see Martin and Stewart)

(ni) "Tubular acanthoma" —This is a name sometimes applied to areas of epidermoid careinoma consisting of narrow ramifying epithelial strands traversing invaded tissues. The name is inappropriate since the strands are solid and do not contain a lumen. Tumours showing this structure are highly malignant, their margins are often ill defined because of the wide zone of microscopic infiltra.

tion, and they frequently metastasize

- (iv) Pseudo glandular structures—Pseudo-glandular structures may be produced by either disintegration of the keratinized centres of epithelial masses (as in Fig 19) or by accumulation of glycogen in the tumour cells. The latter change produces a soft juicy tumour in which pseudo glandular spaces and cysts containing watery fluid rich in glycogen readily develop, and the microscopic appearance of such tumours closely resembles that of clear celled carcinoma of the kidney On p 435 of my 1934 work, under the diagnosis of "richly glycogen containing cystic papillary adenocarcinoma of the skin", I described a bulky fungating tumour of the neck in a woman aged 72, which I now recognize to have been really an epidermoid growth with great accumulation of glycogen (Fig 20) Metastases in the lungs and liver were also rich in glycogen and of similar clear celled and cystic structure.
- (i) 'Adamanimoma' -like structure—This is sometimes seen in ordinary squamous cell carcinoma (Fig 93) as well as in the basal cell tumours of the tibia (see below)

corrugated surface They occur on the face, trunk or limbs they may be solitary or multiple, multiple ones often occurring as a group in a particular region. I have seen a crop of eight of them restricted to the skin of the vulva. Fox has given a good description of these growths and has rightly deprecated the habit of calling them. naevi

Microscopically (Fig. 100) these growths consist of folded thick layers of epithelium clothing slender dermal papillae. The epithelium consists mainly of small cells of basal or baso spinous type with ill defined prickles the cells contain



Fio 100 -Pigmented papilloma of groin from a man aged 62 (× 120)

varying amounts of finely granular brownish pigment. The epithelium also encloses small horny foci or pearls which however are continuous with the horny stratum corneum on the surface of the papilloma. J. W. Dawson apity said of the microscopical structure of these tumours. The appuarances in many cases are difficult to describe so striking is the appearance of the horny pearls and the islets of mesoblastic tissue among the sheets of cells but it is almost as if a thick disc of small epithelial pigmented cells rested on the corrum and mesoblastic cores had canalized it in various directions raising the epithelium into papillae covered with stratum corneum. These growths have nothing in common with pigmented moles no naevus cells are present and when a malignant growth develops in one of them, a rare event this growth is a squamous cell carenooma.

Squamous-cell carcinoma of the skin (epidermoid carcinoma acanthoma, epithelioma)

(a) Mode of origin

Elsewhere (1944 and 1945, and Chapter 7) I have given the evidence that squamous-cell growths of the skin arise not from single minute foci but from fields of prepared epidermis of small or great extent. Study of solitary localized

previously reported cases of caleifying "epithelioma" Of more recent accounts that of Côte is excellent. The name "epithelioma" is misleading—these growths have little in common with epidermoid carcinomas, and it is questionable whether they are really tumours at all. They may be only sebaceous or epidermal cysts with initial irritational overgrowth of the epithelium followed later by degeneration.

(3) Basal-cell carcinoma

This type of growth may arise in the epidermis itself, producing first a plaque like thickening of the skin and later a slowly enlarging ulcer—"Jacob's ulcer"

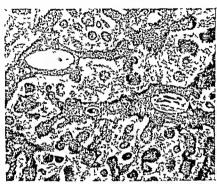


Fig. 101 -Rodent carcinoma of back, showing relationship to degenerating hair shafts (× 80)

(Jacob, 1827) or 'rodent ulcer' Or it may arise, not from the epidermis, but from pilo sebaceous follicles or sweat glands deep in the dermis, producing a non ulcerating well defined rounded or lobulated sub epidermal or subcutaneous growth, variously designated Brooke s tumour', "eystic adenoid epithelioma', 'sub-epidermal benign basal cell tumour' 'turban tumour', etc. As Krompecher long ago showed, no sharp separation between basal-cell growths of the superficial and deep types is possible, growths similar in structure and behaviour may arise from basal cells in any part of the epidermis and its append ages. Good accounts of these tumours include those of Krompecher, Lohmer, Molesworth and Haythorn

(a) Basal cell carcinama of superficial origin (radent carcinama)

(i) Distribution—Most of these tumours occur on the face or neck but any part of the skin may be affected—the trunk, limbs (Newland), vulva (Wilson) anus (Lawrence), etc The specimen depieted in Fig 9 was from the cubital fossa that of Fig 11 from the chest, and that of Fig 101 from the back On the face the most common sites are on the lower cyclids

(c) Local spread

Enidermoid carcinomas of the skin differ widely in their invasiveness. Many of them are of relatively low malignancy growing and penetrating into the underlying tissues only slowly, and no sharp distinction between papillomas and these chronic carcinomas can be made. Typical of the chronic relatively benign kind of carci noma are those of the dorsum of the hand in elderly outdoor workers many of which long remain freely movable on the deep tissues and non-ulcerated Exacerba tions of growth are not unusual a formerly slowly growing well localized tumour taking on more rapidly invasive growth. Such changes in rate of growth of a tumour are sometimes reflected in its structure, part of it consisting of the older well differentiated growth and part of it of younger more anaplastic and more invasive elements (Fig 4) Once a tumour has penetrated through the dermis into the subcutaneous and deeper tissues it often extends more rapidly in these Tumours arising in scars or chronic ulcers usually remain superficial for long periods but they often replace the superficial tissues over wide areas extension widespread cancerous change plays a part as great as or greater than invasive replacement (Willis, 1945). Once a scar cancer has penetrated through the avascular scar tissue into the deeper tissues, it often spreads more rapidly (Treves and Pack)

Deep to and around early carcinomas dermal changes especially in the elastic tissue are prominent. The elastic fibres commonly show great increase in both number and size and degenerative swelling and fusion. The altered elastica is often plainly visible in haematoxylin stained sections as a bluish layer up to 2 or 3 millimetres tluck (Willis 1944).

(d) Metastasis

From most kinds of epidermoid cancers of the slon, metastasis occurs relatively late and infrequently. Shrek found that 16 per cent of these tumours metastasized to lymph glands and that the site of the primary growth did not greatly affect the liability to metastasis. Taylor et al. however found considerable differences lymph nodal metastases from primary growths of the fingers were present in 9 per cent of cases, of the hands 15 per cent ams 26 per cent, feet 41 per cent and leg 36 per cent. In my experience squamous cell cancers of the face and neck frequently produce metastases. X ray cancers though often slow to metastasize eventually do so in a considerable proportion of cases—from 25 to 70 per cent in various reported series (Haagensen Hueper). Osteomyelitis carcinomas rarely metastasize, Bereston and Ney could find only 7 reported instances. Metastases are infrequent also from cancers of sears chronic ulcers and sebaceous cysts. Most metastatic growths from skin tumours are in the regional lymph glands, blood borne metastases are less frequent (for some examples see my 1934 work, p. 416 Treves and Pack, and Cookson).

(e) Note on calcified epithelioma of the skin

There is a group of rare sub epidermal tumours composed of masses of well differentiated corntlying epidelium which undergoes extensive necrosis and calcification. The tumours arise chiefly in young people including children most often in the head neck or arm, they are well defined grow slowly may cease growing and never metastasize. Ossification in the stroma is not unusual a good example of this was described by Nicholson (1917) who also reviewed

the basal layer of the epidermis, with either rounded or angular outlines, the marginal parts of the downgrowths showing a distinct layer of cubical or columnar cells and their centres consisting of small dark-staining polyhedral, ovoid or

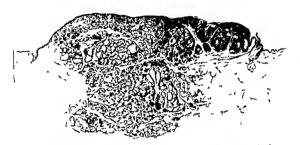
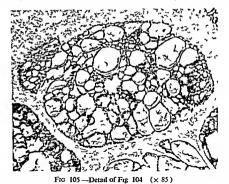


Fig. 104—Superficial but non ulcerated cystic basal-cell growth of back of neck of a woman aged 45 (×6)

fusiform cells devoid of any special arrangement. Inter cellular bridges are usually missing or indefinite, but are sometimes clearly present. Remarkable



in view of the slow growth of the tumours is the presence of plentiful mitotic figures in the cells—the explanation may be that some unknown factor arrests or retards mitosis in the later stages—Minute rounded eyes often develop in

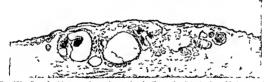
along the side of the nose and across the middle of the cheek. Glasunow and McFarland et al. saw in this distribution a relationship to the embryonic facial clefts and supposed the tumours to be facial cleft carcinoids." derived from developmentally sequestrated cells. No real evidence exists to support this purely



Fig. 102—Satellite focus of origin from basal layer of epidermis at margin of a main growth 3.5 contimetres in diam ter $(\times 85)$

speculative suggestion indeed, the distribution of tumours is opposed to it, for many quite typical rodent carcinomas arise on parts of the face and neck remote from the facial elefts or in other parts of the body. The predilection of the tumours for the middle third of the face and the nasal margins is probably related to the distribution of sebaceous ghads and perhaps to the incidence of light. The studies of Lohner Molesworth Willis (1945) and others, of early super-

free studies of Lonner Molesworth Whits (1945) and others, of early superficial basal-cell growths show unmistakably that these often arise not from single minute foci but from multiple foci in considerable areas of epidermis, and that the basal-cells of hair follicles and shafts and of the skin glands may



Fic 103—Superficial but non ulcerated cystic basal-cell growth of back of an elderly man who had 11 separate similar tumours on various parts of body (× t5)

also participate in the cancerous change (Fig. 101). Clinically multiple tumours on the face or elsewhere are common very numerous tumours on many parts of the body may occur (e.g. Case XIV of my 1945 paper) and microscopical study of the excised specimens will often disclose minute separate foci of growth in the epidermis marginal to the chinically obvious tumour (Fig. 11 and 102). Haythorn particularly stressed the pilo sebaceous origin of basal cell carcinomas and advocated the title. hair matrix carcinomas

(u) Microscopical structure—This is depicted in the figures. The following features may be noted. Many tumours show multiple solid downgrowths from

but they can neither be subdivided into distinct groups, either clinically or histo genetically, nor separated sharply from the superficial basal cell growths of rodent type on the one hand or the truly glandular skin tumours on the other Any subdivision is arbitrary and leaves borderline cases between the sub groups. The multiplicity of names and views advanced regarding non ulcerating cystic basal cell growths of the skin is well set forth by Warvi and Getes, and valuable accounts include those of Krompecher, Savatard (1922 and 1938) and Ronchese

(i) Distribution—Sub epidermal basal cell growths show less predilection for the face and neck than their epidermal counterparts, many of them arise on

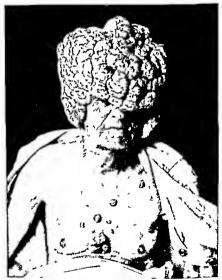


Fig. 107 — Turban tumours in an old woman slowly enlarging since early adult life

the trunk, limbs and scalp A remarkable group of cases exists in which very numerous tumours develop in the skin of the thorax, neck, face and scalp, usually appearing first during adolescence and increasing slowly in size and number Goldsmith and Freudenthal saw a boy of 7 in whom multiple basal-cell growths of the face and neck had first appeared at the age of 5. In Paul and Inglis s case multiple facial tumours were noticed at the age of 2. The disease is often familial, and is commoner in femiles than males. Brooke and Fordyce described cases

the epithelial masses (Fig. 103) and these may become so numerous as to produce conspicuous hone, comb patterns (Figs. 104. 105). Parts of the tumours may thus acquire a spurious glandular appearance. The epithelium often displays also branching reticular and folded patterns (Fig. 106). All of these variations of structure may be seen in one tumour. Metaphasne goblet cell formation occurs occasionally (Nicholson. 1923. and Sikh).

(in) Local spread—The name rodent' is appropriate. The timours are slowly invasive and destructive. Untreated growths on the face may eventually destroy most of the facial soft tissues and bones or may penetrate to the skull or brain. Thanks to prompt radiational and surgical treatment, the frightful destructive power of these eroding timours is now rarely seen. Elsewhere (1930) I have reported penetration of the apex of the lung and of the spinal canal by a



Fro 106 -Reticular structure of basal-cell carcinoms (x 85)

rodent cancer of the neck. There occurs also a type of superficially spreading basal cell carcinoma which does not ulcerate deeply and which tends to heal in parts this is Molesworth's superficial cicatrizing type and Brown and McDowell's field fire carcinoma.

(1) Metastasis — Metastasis of basal cell carcinoma to the regional lymph glands has rarely been seen (Beadles Functud Mulzer). The only acceptable report of metastasis by the blood stream is that of De Navasquez who saw deposits in the lungs and bones from a structurally typical basal-cell tumour of the forehead. Niles s case of supposed basal cell epithelioma. Youth metastases is unacceptable the figures show an active squamous-cell growth.

(b) Basal cell growths of sub epidermal origin

Sub epidermal basal cell growths arising from the pilo sebaccous epithelium and the sweat glands are of very variable structure distribution and behaviour.

clearly contributing nothing to it, but in other cases basal cell downgrowths from the epidermis co exist with the sub epidermal masses of tumour, as in Fig 9. The shape and structure of some "rodent ulcers" suggest the supervention of surface ulceration in a predominantly sub epidermal tumour.

(.11) Growth—Growth of the sub-epidermal basal cell tumours is slow and expansive in type. They do not infiltrate surrounding tissues, and ulceration takes place only accidentally, or because the tumour includes superficial growth



Fig. 109—Detail of Fig. 108 showing that the small turnour clumps are sweat glands filled and distended by solid basal-cell growth (× 90)

of "rodent" type Metastases never develop These characters explain the "benign" reputation of the group Streitmann's interpretation of a quiescent lymph nodal metastasis of 15 years duration in his case of Spiegler tumours is dubious, no lymphoid tissue was found around the supposed metastatic growth, which may have been one of the multiple primary tumours unusually situated in the supraclavicular region

(c) Mixed basal cell and squamous cell carcinoma

While most carcinomas of the skin are readily classifiable as of either squamous-cell or basal cell type tumours of intermediate structure and behaviour occur (Krompecher, MacCormac, Darier, Montgomery, Brown and McDowell) Some tumours show separate areas of the two types of growth, others show throughout an intermediate or combined structure, i.e. the general structure of basal cell carcinoma but with scattered cell nests or areas of distinct spinous cells (Fig. 114) Such tumours maintain their intermediate structure in their lymph nodal or blood borne metastases (Willis, 1930) Patients with multiple tumours, some squamous celled and others basal celled, may also have tumours of intermediate or mixed type (Brown and McDowell) Mixed tumours may develop in cases of xeroderma pigmentosum (Geschickter and Koehler)

in which the tumours were distributed mainly on the face and chest and this syndiome is often designated Brooks or Fordyces of disease. Brooks a name of epitheloma idenoides cysticum is frequently used for growths of this type. When the tumours predominate on the scalp as in the case depicted in Fig. 107 they are 'Spiegler's tumours' or "turban tumours' (Ronchese). The following case is noteworthy.

Case V (Mr. A.F. Maclare's case)—An unmarried woman first came under observation at the age of 40 with numerous rounded sub-epidermal growths measuring up to 2 centimetres in diameter scattered over the scalp face neck and upper part of the thorax. These had first been noticed at the age of 20 and had slowly increased in size and number An interesting feature was that none had developed in the area of a childhood burn sear on the neck. No family history of skin tumours was given. A tumour excised from the skin of the chest showd the typical structure of a cystic bassl-cell growth clearly related to sweat glands.

Cases with solitary or few non-familial tumours of similar type are quite common the tumours usually not appearing however, until middle age (see Figs. 108 109)



Fig. 108 +Solitary sub-epidermal mainly solid basal-cell growth from scalp of woman aged 45 (\times 7)

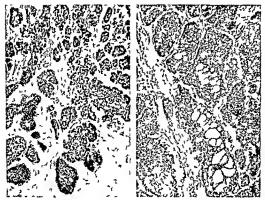
(h) Structure—(Figs 9 10 108 113) The tumours consist of well defined masses of closely packed dark staming epithelial cells generally resembling those of rodent careinomas. In young tumours the appearance of smaller masses often points to their origin in one or more groups of sweat glands (see Figs 9 10 108 and 109 and Ronchees s Figs 7 and 8) in their shape and distribution the epithelial clumps resemble sweat glands or ducts filled and distended by tumour cells in situ and the presence of thick hyaline basement membranes around them often enhances the resemblance to sweat glands. Evidence of the participation of sebaceous glands and hair follicles may be present also, but is less frequent. The larger masses of epithelium show cystic changes, pseudo glandular structures, and sometimes the reticular and laciform patterns more commonly seen in rodent careinomas. The surface epidermis is often intact and unaltered over the tumour,

The occurrence of tumours of intermediate type serves to remind us that the basal cells and spinous cells of the normal epidermis are not sharply distinct and that the former also possess intercellular bridges. Pathologists, by their nomenclature, have over emphasized the distinctions between basal cell and spinous cell growths the truth is that these are only variants of one histogenetic group of tumours, and it is a matter for surprise that tumours of mixed structure are not more frequent than they are

(d) Basal cell carcinoma (" adamantinoma") of the tibia

Less than a score of examples of this rare tumour have been reported, including those of Fischer, Baker and Hawksley, Richter, Ryrie, Holden and Gray, Rehbock and Barber, Wolfort and Sloane, Oberling et al., Thomas, and Petrov and The lesion is a distinctive one A slowly-growing tumour develops in the middle or lower third of the shaft of the tibia, skiagrams of which show a well defined area of bone destruction, sometimes occupying the centre of the bone, sometimes appearing as an eccentric defect usually of the anterior part of the shaft Dissection reveals that even in cases in which the radiographic appear ances showed a prominent central lesion, the tumour also involves the surface However, from many of the cases reported, it is clear that the tumours originated in the periosteum or bone and not in the overlying skin or soft tissues, for these were unaffected Most of the patients have been middle aged males, but Richter's patient was a 12 year old Javan boy, and Thomas's patient was a girl aged 19 who had had a lump in her shin since the age of 12 In most cases there has been a definite history of previous injury to the area but not a severe or penetrating injury Petroy and Glasunow refer to a similar tumour in the ulna of a woman aged 22 described by Maier

- (1) Microscopical examination —Microscopical examination shows an epithelial growth usually of distinctly brisal cell type, but sometimes, as in Rehbock and Barber's case, with cell nests or other epidermoid characters. A loosely reticular arrangement of the cells in the centres of the epithelial masses in some of the tumours has resembled that seen in "adamantinomas" of the jaws, and it was this feature which led the first describers of these growths (Fischer, Baker and Hawksley and Ryrie) to call them "adamantinomas" of the tibia. The propriety of this name, however is more than questionable not only is there no warrant (save an occasional structural resemblance) for regarding the tibial and the oral tumours as related but the name 'adamantinoma is inappropriate even for the oral tumours themselves (see Chapter 16)
- (i) Histogenesis—Two views must be considered (a) that the tumours arise from developmentally misplaced islands of epidermal cells in the periosteum or bone (Baker and Hawksley, Petrov and Glasunow) or (b) that they arise from cells of the epidermis or its appendages displaced into the periosteum by trauma (Ryrie). Those favouring the first view point to the difficulty of imagining how non penetrating injuries could dislocate adult epidermal cells into the periosteum while those advocating the second view point to the usual history of definite injury in the cases and to the superficial position of the tibia immediately beneath the skin. Ryric thought it quite possible that shearing injuries in this region might detach deep hair-follicles from the epidermis and that during repair such fragments might become incorporated in the bruised periosteum. This



Fro 110 —Solid and cystic basal-cell growth from solitary sub-epidermal tumour of neck of a man aged 59 $(\times$ 80)



Fig. 111 —Part of a pedunculated sub-epidermal cystic basal-cell growth of arcola of nipple of a man aged 50 $(\times 6)$

sweat-gland tumours, a tumour predominantly of solid or cystic basal cell type may contain areas of acinar structure (Figs. 112, 113), and vice versa. Further, attempts to subdivide sweat glandular tumours into 'syringomas supposed to have arisen from the ducts, and "spiradenomas" or "hydradenomas" supposed to have arisen from the secreting acini, or to segregate cystic members of the group under such captions as "syringocystadenoma", are unjustified and unnecessary. The adenomas and adenocarcinomas of sweat glands and ducts form a single group, the variants of which do not call for special names. There is no need either to separate sweat glandular and apocrine tumours. (For a useful description and review with many references, see Gates, Warren and Waru)



Fig. t13—Detail of Fig. 1t2 showing sweat glands continuous with or differentiating from solid basal-cell growth. (× 170)

The tumours may be solitary or multiple, and may affect any part of the skin especially the scalp, face, chest, axillae, vulva and buttocks. They are not unusual on the hands or feet. They may appear at any age but are most frequent in the middle aged or clderly, women are affected more often than men. In one group of cases, multiple tumours of the trunk have appeared about puberty, usually in girls, and it has been suggested that these are related to some developmental anomaly of the glands.

(i) Structure—(Figs 94, 115) The tumours usually form well defined but not encapsulated growths in the dermis or subcutaneous tissues. They may show a well developed acinar structure resembling that of sweat or apocrine glands, or they may be predominantly cystic papilliferous or solid. The stroma is variable in amount, it may be abundant, and may show peculiar hyaline or mucoid changes. Simard described an unusual tumour of the palm which had a pleomorphic structure recalling that of a salivary tumour, including not

suggestion is I think plausible careful microscopic study of the tissues of searred adult shins might clarify it Krebig saw a shin tumour of pleomorphic structure like that of the salivary tumours unattached to either the skin or bone

(iii) Growth—The tumours grow slowly and metastasis to the inguinal lymph glands has been proved in only one case (reference by Petrov and Glasunow) Adequate local excision or amputation is usually curative

(4) Tumours of glandular structure arising from sebaceous glands

Warren and Warvi have reviewed the hyperplasias and tumours of sebaceous glands. Hyperplasias such as rhinophyma should be distinguished from tumours,

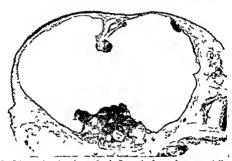


Fig. 112 -Solitary sub-epidermal cystic basal-cell growth of arm of a man aged 69 (x 6)

so also should the enlargements of sebaceous glands—'sebaceous naevi —accompanied by other developmental anomalies in Pringle 5 disease. True sebaceous adenomas and adenocarcinomas are rare. Most of them occur on the eyelids face or scalp in middle aged or old subjects, either men or women. Those of the eyelids arise from the Meibomian glands. The tumours grow slowly distending the overlying epidermis, ulceration is usually long delayed, and metastasis to the regional lymph glands infrequent. Warren and Warvi point out that only small areas of a carcinoma may show typically sebaceous structure and the tumour may be mistaken for an ordinary squamous cell or basal cell growth. Indeed, it is needless to distinguish sharply between sebaceous tumours and basal cell or squamous cell growths arising partly from pilo sebaceous units, these differ not in histogenesis but only in the kind of differentiation they show. Innis and Whittick saw an adenocarcinoma of the Meibomian glands in a dog

(5) Tumours of glandular structure arising from sweat glands

Sub epidermal basal cell growths of sweat glandular origin have been described above. No sharp distinction can be drawn between these and adenomatous

not be distinguished from basal cell carcinomas", and that several recorded sweat gland tumours "present difficulties of interpretation, because of atypical

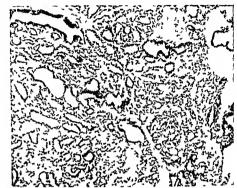


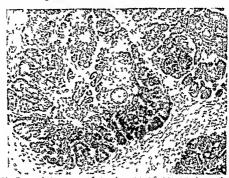
Fig. 115 -Sweat glandular adenoma of finger from a man aged 72 (x 100)



Fig. 116—Squamous metaplasia of sweat glands and ducts from multiple small papular lesions of skin of front of chest of a woman aged 22 present since childhood (× 120)

characteristics such as pearl formation. For reasons already given, I believe that it is impossible to make sharp histogenetic and structural distinctions between

only glandular tissue but also squamoid areas, mucinous secretion and pseudo cartilage. Simard regarded the growth correctly in my opinion as a tumour of sweat glands in which the cells had acquired mucus secreting functions but it is not necessary to assume with him that there was a metaplasia of epithelial tissue into cartilage. (See Chapter 17) Myo epithelium certainly occurs in some well differentiated sweat gland tumouts but the descriptions and figures of some writers e.g. Sheldon, are unconvincing.



Fro 114 —From redent careinomia of nose showing confishcation in predominantly basal-cell growth (× 85)

The following case is notable not only because the tumour showed combined glandular and basal cell structure but also because of its unusual history and stitution

Care VI—In 1918 a girl aged 18 had a subcutaneous tumour 15 centimetres in chameter removed from the volar aspect of the distal part of her thumb this proved to be a synovioma of fibrous and giant-celled type. In 1943 a tumour of several months duration was existed from the same situation. This proved unoperceptily to be a carrinorma partly of typical basal-cell structure partly of epidermoid structure and partly of agent structure clearly derived from swest glands. Were the 2 tumours quite innetiated and concidental or is it possible that some carenogenic stimulus perhapi related to a penetrating injury may have evoked successive neoplassis in 2 distinct assues? The patient was a seamstress but did not regall having pricked her thumb

Gates et al sharply distinguished sweat gland tumours from basal-cell tumours and held that the origin of basal-cell carcinomas from the sweat glands is unlikely on theoretical grounds and has yet to be proved. Yet they admitted that in some sweat gland tumours the typical appearance is not seen and there may be a close resemblance to basal cells or squamous cells. It that in some tumours the structure has a certain resemblance to hair matrix carcinoma that thurteen of our tumors were from both sweat glands and har follieles, that it is quite possible that undifferentiated carcinomas of sweat glands may

of finely papillary growth clearly derived from the sweat ducts

Babes and

Kaufmann described cases, and the following is another example

Case VII (Mr. A. F. Maclure's case) —For several months, a woman aged 60 had noted a slowly enlarging harriess moist patch on her scalp, this showed a well defined circular area. I centimetre in disanteer in which the epidermis was replaced by a soft villous pink tissue. Sections of the excised area showed a finely papillary growth clothed by a double-layered epithelium resembling that of the sweat ducts (Figs. 117–119). The subjacent dermis contained large dense collections of lymphocytes.

(n) Growth —Most sweat-gland tumours grow slowly and non invasively A disorderly structure does not necessarily denote malignancy Papillary or solid growths have often been dubbed "adenocarcinoma" because of their disorderly structure and the absence of a capsule, but they seldom recur after



FIG 119 — Case VII Sweat glandular papilloma of surface of scalp Enlarged view of part of Fig 118 (× 250)

removal However, a few genuinely malignant infiltrating tumours have been observed, with occasional metastasis to the regional lymph glands (references by Gates at al)

(6) Tumours of other special glands

It is convenient to mention here the rare adenomas and adenocarcinomas of the ceruminous glands (Montpellier and Laffargue, Warren and Gates), and of the lachrymal and tarsal glands (Flick, Ziporkes Tille and Leroux Robert) The lachrymal tumours often show a close structural resemblance to salivary tumours (Fig 120) For tumours of the lachrymal caruncle see Evans and of the lachrymal sac Penman and Wolff and Spratt

the basal cell and glandular types of growth arising from the sub epidermal appendages of the skin Many transitional and 'atypical' tumours occur, our



Fig. 117—Care VII Sweat glandular populisms of surface of scalp. General view showing replacement of epidermis by papillary growth (P) and collections of lymphocytes in dermis (L) (× 10).

sub groups made according to the predommant structure in the individual tumours, have descriptive value but are arbitrary. It is noteworthy that the sweat glands and ducts can undergo squamous metaplasia in non neoplastic lesions (Fig. 116).



Fig. 118—Case VII Sweat glandular papilloma of surface of scalp Details of Fig. 117 note the double layer of epithelial cells. (× 80)

A very rare type of sweat glandular tumour remains to be mentioned This takes the form of a replacement of the surface epidermis by a pink velvety layer

Structure (Figs 121 123) —The epidermis is thickened and the interpapillary processes broad and blunt. The cells, especially of the spinous layer, show great irregularity of size and shape, including grant or multinucleated forms. Mitotic figures are plentiful, and many of the nuclei are hyperchromatic or distorted Large rounded pale or vacuolated cells, resembling those of Paget's disease, are often present. The surface may or may not show excessive keratosis. The dermis shows chronic inflammatory changes and abundant lymphoid and plasma cells.

The following are my personally studied cases

Case VIII — Male 70 Multiple patches on the back of many months duration (Figs 121 and 122)

Case IX—Male 70 Single patch 2.5 cenimetres in diameter on dorsum of forearm of 6 years duration (Fig. 123)

Case X—Male 55 Fair skinned man always very sensitive to sunburn, has had many keratoses of the face for years Plaque like rough area 2 centimetres in diameter developing behind ear for 2 years failed to respond to repeated radium applications therefore excised Structure closely similar to that of Case IX

(b) Extra mammary Paget s disease

Paget's disease of the nipple is described in Chapter 13 From time to time extra mammary lesions resembling the nipple disease clinically and more or less histologically have been described. The earliest reports were those of Paget himself Crocker, and Rolleston and Hunt. Paget's original reference to chronic balanitis followed by cancer is cited in Chapter 13, and he too concurred in the diagnosis of Crocker's case of Paget's disease of the scrotum and penis. Rolleston and Hunt's case also was one of clinically typical Paget's disease of the public and scrotal skin, in which the epithelial cells formed 'psorospermoid bodies' resembling those described by Darier For more recent reports of cases of extra mammary Paget's disease, see references by Inglis, Weiner, and Stout Weiner pointed out that all acceptable examples of extra mammary Paget's disease were from the axillae or ano genital regions, i e regions where apocrine glands occur

With the recognition and naming of Bowen's disease, uncertainty arose as to the distinction between this and extra mammary Paget's disease. Some workers, e.g. Inglis, distinguish sharply between them mainly on histological grounds, others like Savatard regard them as identical, or at least as only forms of the same disease. For reasons already given in Chapter 13, I adopt the latter view. In my opinion, Bowen's disease and Paget's disease are not sharply separable histologically each may show areas resembling the other, and in particular Bowen's disease often shows rounded pale or vacuolated cells indistinguishable from Paget cells. The predominance of such cells in Paget's disease of the nipple and the usually greater bulk of the epidermis and its more pleomorphic cytology in Bowen's disease, are not sufficient grounds for their sharp separation.

Stout has reviewed the few reported cases in which the picture of Paget's disease has been produced by growths possibly of the nature of amelanous melanomas. It is suggested that these cases form a group of superficial slow growing naevo carcinomas with Paget like characteristics which distinguish them from other melanomas. Should future work verify this, the conception of the essential unity of all forms of epidermal carcinoma an situ will not be invalidated.

melanomas also are epidermal growths

(7) Intra epidermal carcinoma

Several related diseases which were formerly regarded as "pre cancerous dermatoses' are to be looked on rather as forms of intra epidermal carcinoma. These are Bowen's disease Paget's disease Queyrat's erythroplasia, and some eases of vulval leucoplakia or kraurosis (References by Inglis, and Mackee and Cipollaro)

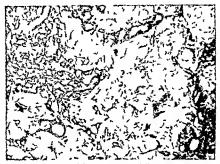


Fig. 120—Adenoma of tarsal gland from a woman aged 40 the small well defined tumour had been present and slowly enlarging for 2 years (× 80)

(a) Bowen s disease

Bowen s disease appears in any part of the skin of middle aged or elderly subjects of either sex as slightly raised reddish brown papular or plaque like lesions with crusted or eroded surfaces. The patches are often multiple in the



Fig. 121 -Case VIII Bowen's disease early lesion. General view. (×8)

affected region they slowly enlarge and may coalesce to form extensive irregular areas. After a long period usually many years, invasive squamous-cell carcinoma develops and metastasis occurs. Kuznitzky and Jacoby report a good example of this sequence.

(c) Erythroplasia

What has just been said of Bowen's and Paget's diseases applies also to Quevrat's erythroplasia or crythroplakia (references and illustrations by Mackee and Cipollaro) This is a rare affection of the glans and prenuce, vulva or mouth characterized by single or multiple shiny or velvety red areas in which frank carcinoma eventually develops. Microscopically the patches show epidermai thickening with ' dystrophie' prickle cells I can see no grounds for regarding this lesion as a distinct entity Paget's "long-enduring balanitis" ending in cancer, later workers' Paget's disease" of the genitalia, "Bowen's disease" of the same regions, and "erythroplasia" are surely no more than variants of one thing



Fig 123 - Case IX Bowen's disease later lesion, general view (x 8)

(d) Conclusion

It remains only to add here that in some cases what appears to be vulval leucoplakia or kraurosis proves microscopically to be already intra epidermal carcinoma resembling Bowen's disease (Chapter 32) This, then, is but another variant of the same disease Different cases show somewhat different clinical and microscopical appearances according to site causation, preceding or associated lesions, and individual peculiarities of the skin Dermatologists have tried to define these differences, by the use of such words as "hyperkeratosis' ' parakeratosis , "dyskeratosis" etc , while different appearances of the lesions have been over emphasized by eponymous labels. But distinctions so created are quite arbitrary and without pathological value. For the pathologist there is only one entity intra-epidermal carcinoma, which, like intra duct carcinoma of the breast may long remain confined within epithelial boundari's Also like intra duct carcinoma, intra epidermal carcinoma shows many structi ral variations, but these do not denote distinct forms of tumour nor call for disting tive names,

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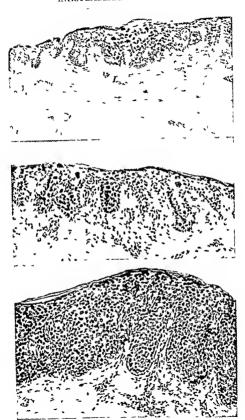


Fig. 122 —Case VIII Bowen's disease early lesson. Details of Fig. 121. A = \times 85. B and C $_{\rm T}$ = \times 144.

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one third of the cases About 6 per cent of oral cancers in betel chewers occur on the lips (Orr), many of these are on the mucous membrane of the maer surface of the lips near the angle of the mouth

(a) Tobacco smoking

That pipe smoking can be causative seems probable from the records of cases in which cancer has developed just where long-standing irritative changes from an habitual position of the pipe has been present, and from the prevalence of cancer of the lip in women in communities where the women smoke pipes. Thus it is said that Irish peasant women and negro women who smoke clay pipes often get cancer of the lip (references by Hueper), and Ahlbom noted that S0 per cent of the lip cancers in Swedish women were in pipe smokers. The risk of pipe smoking with its tarry products, heat and mechanical irritation, might be suspected prima face, and Flory and Roffo have shown that tobacco tar is indeed carcinogenic. Thus, there are good grounds for concluding that pipe smoking is a causative factor for lip cancer and that it probably acts by means of chemical carcinogens, perhaps aided by mechanical or thermal injunes to the tissues (see Chapter 4). The part played by eigarette-smoking is much more debatable, and the evidence inconclusive

(b) Sunlight

Sunlight has been blamed as an important cause of lip eancer, e.g. by Haagensen and Molesworth. Thuse workers point out that this factor would explain the sex incidence of the disease, its disproportionate frequency in farmers, fishermen and other outdoor workers, and its high frequency in sunny countries like Australia. Molesworth recorded that with rare exceptions his Australian cases showed clear evidence of chronic sumburn, often including keratoses of the lip and other parts of the face. The great preponderance of tumours of the lower lip is explained as due to direct exposure of its muco cutaneous junction to sunlight, while the corresponding part of the upper lip is relatively shaded. The proved importance of sunlight in the causation of skin cancer also makes a strong case for its importance in lip cancer.

(c) Exposure to tar, pitch or oil

This is certainly another causative factor in certain occupations (reference by Hueper). A peculiar instance of such exposure is in the net fishers described by Shambaugh. These men, when mending their tar impregnated nets, have the habit of holding the tar smeared wooden needle between the lips the lips visibly retain smudges of tar for long periods. Since Beck experimentally proved the carcinogenic properties of the tar mixture used by the fishers the evidence is strong that the fairly frequent lip cancers encountered amongst them are due to this cause.

(3) Structure

Most of the tumours are of ordinary cornifying squamous cell type (Figs. 12 and 124). A few of them show predominant "tubular acanthoma" or poorly differentiated anaplastic growth. Study of early tumours shows that they arise

CHAPTER 15

EPIDERMOID CARCINOMAS OF THE LIPS, MOUTH, PHARYN\ AND LARYNY

THE EPITHELIAL tumours of the oropharyngeal region comprise the following

- (a) Papillomas of the surface epithelia
- (b) Epidermoid carcinomas of the surface epithelia
- (c) Tumours of the dental shelf tissues
- (d) Tumours of salavary and other glandular tissue

The surface papillomas are infrequent and show no specially notable features, tumours of the derivatives of the dental shelf are described in Chapter 16 and salivary glandular tumours in Chapter 17. The present Chapter is concerned with the epidermoid carcinomas of the surface epithelia in different situations these growths differ somewhat in causation structure and behaviour, yet they have much in common and are best considered together

FPIDERMOID CARCINOMA OF THE LIPS

For good accounts of incidence causation and pathology, see Lane Claypon (1930), Newell (1939) and Martin et al (1941). In analysing the properties of cancer of the lip only growths of the muce cutaneous junction should be considered basal cell growths of the labial epidermis should be excluded, since, as Newell's paper shows, these differ strikingly from epidermoid carcinomas in site and sex incidence.

(1) Age, sex and site incidence

The mean age of patients when they first come under observation varies in different series from 52 to 65 years with a general average of about 57. Two-thirds of the cases are between 50 and 70 years of age. The mean age at death of fatal cases in 70. The disease is very rare in youth, New and Hertz reported it in a boy of 13 years.

Of Lane Claypon's collected 4 839 cases 93 5 per cent were males, a sex ratio of 14 to 1. In Pack and Le Feyre's series the ratio was 16 to 1.

The lower lip is far more frequently affected than the upper, the percentages in the series of Lane Claypon Newell and Martin et al being 94, 95 and 93 respectively. The disproportion is much less for females than for males in women nearly one quarter of the tumours are in the upper lip but in men only 36 per cent of them (Lane Claypon). This difference points clearly to the operation of different causative factors in men and women. (See Ahlbom's (1936) work discussed later).

(2) Causative factors

There is little or no evidence that syphilis alcoholism and dental irritation are important causative factors. Non syphilitic leucoplakia is present in nearly

The percentages of males in Lane Claypon's, Pack and Le Fevre's, and Morrow's series were 90 87 and 84 respectively

In nearly two thirds of the cases the tumours arise along the lateral margins of the tongue—the remainder on the dorsum, under-surface, base and tip in that order of frequency

(2) Causative factors

Alcohol tobacco, dental disease and hot food have often been blamed as causative, but, while any or all of these may indeed play a part, proof is difficult

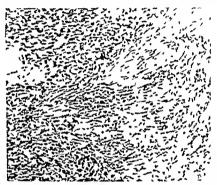


Fig. 125—Diffuse spindle-celled growth at the invading edge of a carcinoma of the tongue (× 120)

to obtain The tongue holds third place in the list of sites of oral can er in betel chewers. The palate and tongue are the two commonest sites of oral cancer in Indians who smoke eigars with the lighted end inside the mouth (Kini). The Plummer Vinson syndrome as a precursor of female oral cancer generally is discussed later.

Syphilitic glossitis

This condition usually with leucoplakia is the most clearly established single causative factor in European males. Of course its frequency in different series of cases varies. Fournier's figure of 84 per cent was certainly an over-estimate, as his practice was principally amongst syphilitie patients, unselected series have shown serological or other evidence of syphilis in percentages ranging from 17 to 42 (Lund Morrow). For the relationship between syphilis leucoplakia and oral carcinoma see Power Lane-Claypon and Stewart.

from fields of predisposed tissue which include both epidermis and mucosa, and sometimes a tumour displays clear structural evidence of this dual origin (See Fig. 12.)

(4) Growth and metastasis

Many of the tumours grow slowly and metastasize late, following simple V shaped excision or effective radiational treatment of early tumours prognosis

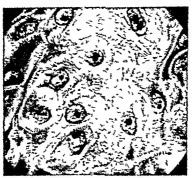


Fig. 124 - Spinous cells in carcinoma of lip. (x 1 000)

is favourable. But in a large proportion of eases the growths are of many months duration when advice is first sought and in some of these metastases are already present in the submaxillary or submental lymph glands (Newell). In late stages, metastases are common in lymph glands and blood borne metastases are not unusual. Remote metastases were present in 4 of 14 neoropsy cases recorded by Martin et al. and in 2 of my 7 necropsy cases (Willis 1944, Cases 45 and 287).

EPIDERMOID CARCINOMA OF THE TONGUE

Good accounts include those of Power (1919), Lanc Clavpon (1930) and Morrow (1937)

(1) Age, sex and site incidence

The mean age of patients is about 54 and nearly two thirds of the cases are in the sixth and seventh decades. The mean age of fatal cases is about 61 years. The disease is rare in young people but has been seen occasionally in children and even in the newly born (Frank et al. Saleeby). New and Hertz reported patients of 13 and 22 years.

Metastatic growths in the neek may be the first signs of small posterior lingual carcinomas. This applied to Cases 31, 122, 154 and 283 of my 1934 work, in three of which the primary growth remained undiscovered during life and was revealed only by careful necropsy. The earliest metastases are usually in the upper deep cervical lymph glands along the course of the great vessels, and, if the primary tumour is undiscovered, these metastases are not unusual. The cervical growths spread from gland to gland of the carotid chain, and eventually form large fused masses enveloping the vessels and frequently occluding or invading the jugular vein. Few nowneed cases of lingual cancer are without multiple cervical metast uses.

(b) Blood borne metastases

These were present in 8 of my 20 necropsies (40 per cent), and Martin et al recorded the same percentage in 50 necropsies. The organs affected are most frequently the lungs and liver, but other sites include the myocardium, kidneys, adrenals bones spleen muscles and skin (Fig. 126). Most cases with remote metastases show large cervical metastases with invasion of the jugular vent, Fleming however, reported a remarkable case in which there were numerous metastases in many organs but the cervical lymph glands were not affected

EPIDERMOID CARCINOMA OF THE CHEEK PALATE AND MOUTH FLOOR

(1) Age, sex and site incidence

In Europeans the average age is about 59, and half of the cases occur in the fifth and sixth decades (Martin and Pflueger) Carcinomas in betel-chewers and in the Indians who smoke eigars in the reversed position occur at earlier average ages, thus 44 per cent of Orr's cases were in the fifth decade and the mean age of Kini's cases was 42 5 years

Martin and Pflueger's series of 99 cases of cancer of the cheek comprised 90 men and 9 women Betel chewer's cancer also is usually commoner in men than in women (Orr), but the sex disparity is much less marked than in buccal cancer in Europeans, and it varies markedly in different communities Betel cancer is particularly common among Filipino and Cingalese women, who suffer from it as much as or even more than the men (Maxwell Vedder Spittel)

In Europeans cancer affects the cheek, mouth floor and palate in that order of frequency Betel chewer's cancer is most frequent on the cheek or lower jaw opposite the molar and premolar teeth where the quid is carried but other parts of the oral cavity are also affected. Thus in Orr's series the sites were cheek 296 cases lower jaw 196, tongue 96, upper jaw 41, lips 40 cases. The distribution of oral cancers in an Indian community who smoked cigars with the lighted end in the mouth was palate 52 cases, tongue 50, cheek 26, fauces and pharjax 14, jaw 13 (Kim)

(2) Causative factors

Unequivocal carcinogenic factors like the betel chewing or reversed

(3) Structure

Most of the tumours show cormfying squamous cell structure of varying degrees of differentiation (see Figs 13 and 126). A few tumours however, show marked anaplasia with loss of recognizable epidermoid characters (Figs 18 and 125). This is more frequent with growths of the base than with growths in other parts of the tongue. Occasional tumours of the base have the structure of 'lympho-epithelioma', more frequent in the nasophatynx (q v)



Fig. 126 -Metastasts of cornifying epidermoid carcinoma of the tongue in adrenal gland (x 80)

(4) Growth and metastasis

Careinoma of the tongue is a much more malignant tumour than carcinoma of the lip growth is often raoidly invasive and early metastasis to the upper cervical lymph glands is frequent

(a) Metastases in lymph glands

Many patients already have lymph nodal deposits when they are first seen Early deposits are certainly embolic, for no tumour is demonstrable between the growth in the tongue and the glandular deposits and occasional cures have been obtained by local excision of the primary tumour and of the affected glands. The following case exemplifies this result

Case I—A woman 69 years of age presented herself in 1928 with an ulcerated cartenoma I centimetre in diameter on the left lateral border of the anterior part of the tongue and a palpably enlarged submaxillary lymph gland. Excision of the primary numour along with a large part of the affected half of the tongue was performed and the hymph glands on the left side were removed. Microscopically both showed cornifying squamous-cell carcinoma. The patient remained well until 1945 when at the age of 86 she died of broncho-piciumous.

is remarkable in that it predominates in women, 90 per cent of Ahlbom's cases and all of the 29 patients seen by Pilcher were women

While tumours of any structural variety may occur in any part of the pharynt or fauces particular variants predominate in particular situations. Most care nomas of the tonsils fauces and lower part of the pharynx are squamous-celled, while in the nasopharynx the so called lympho epitheliomas and transitional cell carcinomas predominate. The commonest site of nasopharyngeal growths is in the lateral wall close to the Eustachian orifice so that unilateral deafness is a frequent early symptom. The pyriform fossae are the commonest sites of hypopharyngeal growths. Carcinomas of the Eustachian tube and middle ear have been described by Stewart and Lieber, and by Rosenwasser.

(2) Causative factors

The incrimination of external agents such as alcohol, tobacco or hot foods is even more uncertain than in tumours of the oral cavity. Digby et all suggested that the very high incidence of nasopharyngeal carcinoma at a relatively early age in Hong Kong Chinese and other orientals might be due to the prolonged inhalation of smoke from lamps fires and tobacco in the badly ventilated native houses but of course this is uncertain. There is no evidence that syphilis is important in causation. Chronic tonsillatis is thought to predispose to tonsillar carcinoma (Cappell) and many of the reported cases of middle car carcinoma have given histories of long-standing infection (Rosenwasser)

The Plummer Vinson syndrome

As a precursor of carcinoma of the pharynx, and also of the mouth and oeso phagus in women this condition has been emphasized particularly by Ahlbom This syndrome which is nearly confined to women consists of dysphagia and anaemia often accompanied by achlorhydria The dysphagia appears to be due to atrophic changes in the oral and pharyngeal mucosa perhaps with accompanying reflex muscular spasm Several patients with this syndrome and with multiple carcinomas of the oral cavity arrested the attention of Swedish workers, and search then showed that the syndrome or simple achlorhydria was present in about 70 per cent of cases of oropharyngeal or oesophageal cancer in Swedish women and that in cases of post cricoid carcinoma the proportion was 90 per cent In Sweden oropharyngeal carcinoma occurs with about equal frequency in men and women and it is clear that alcohol and syphilis are relatively unimportant factors in causation and that the most important single predisposing factor is the nutritional disorder which expresses itself as either the Plummer-Vinson syndrome or as simple achlorhydria. The relative importance of this factor in other communities has still to be decided

(3) Structure

Most pharyngeal and faucial growths are epidermoid carcinomas of the well-known type though many of them are structurally atypical and anaplastic (Wills 1930) In 1921 Regaud and Schmincke proposed the name 'lympho epithe lioma to distinguish a group of highly radio sensitive tumours most frequent

cigar smoking of oriental communities are seldom identifiable in European cases In their series of cheek cancers Martin and Pflueger found that signs of chronic irritation or leucoplakia were frequently present but as with other oral cancers the degree of importance to be attached to particular factors such as dental irritation syphilis, smoking and the Plummer Vinson syndrome remains un certain

The careinogenic substance responsible for betel chewer's cancer is still to be identified. The quids consist of mattures of buyo leaves. Areca or betel nuts slaked lime tobacco and spices. The composition of the quid varies in different countries and districts, and this probably accounts for the marked differences in the frequency of betel cancer in different localities. Thus, betel chewing is a common habit but betel cancer is of low medience in Formosa Guam and the Dutch East Indies, while in Madras Malabar Coast, Travancore, Ceylon and the Philippines betel cancer is a very frequent, in some localities the most frequent kind of malagnant disease. For further discussion see Khanolkar, 1944

(3) Structure and metastasis

The tumours are of cormfying epidermoid type, with varying degrees of differentiation. Highly anaplastic growths are rare. In their local spread and their metastasis these tumours generally resemble lingual cancers but are on the average slightly less malignant. In Martin and Pflueger's 99 cases metastases developed during the course of the disease in 51, in all but 11 of which the metastases appeared to be restricted to the submaxillary fymph nodes.

EPIDERMOID CARCINOMA OF THE TONSILS AND PHARYNX

For useful accounts see Trotter (1911) New (1922), Quick and Cutler (1927) Willis (1930) New et al (1932) Ahlbom (1936) Cappell (1938), and Godtfredsen (1944)

(1) Age sex and site incidence

As with the oral carcinomas more than half of the pharyngeal carcinomas occur in the sixth and seventh decades. The age medicance is related to the type of growth, those of the Jimpho epithelioma 'type occurring earlier than those, of squamous cell type. In Godtfredsen's series of over 400 nasopharyngeal tumours the average age of patients with carcinomas was 51 years and of those with "sarcomas (mainly lympho-epitheliomas, no doubt) 46 years. Three of Cappell's 12 lympho-epithelioma cases were under 30 years old namely 21, 23 and 25 and he refers also to cases in children aged 8 and 12. The mean age at death of 27 cases of squamous cell carcinoma of the pharynx on which I performed necropises was 64. Digby et al. reported 114 cases of nasopharyngeal carcinoma in Chinese in Hong Kong. these showed a relatively early age incidence the peak of the distribution curve being in the fourth decade.

Squamous cell careinomas of the pharynx and tonsil show a decided prepon derance of males my 27 necropsy cases comprised 20 men ind 7 women in Pack and Le Fevre's series the sex ratio for tonsillar cureinomas was 10 to 1 Lympho epitheliomas show a less unequal sex incidence. Post ericoid careinoma.

the neck as well as blood borne metastases, Godtfredsen recorded distant metastases in 19 per cent of his entire series, in 27 5 per cent of his fatal cases, and in 18 of 47 necropsies (38 per cent)

EPIDERMOID CARCINOMA OF THE LARYNX

An early but good account of laryngeal cancer was that of Butlin (1883), see also Thomson and Colledge (1930) on the clinical aspects, and Kaufmana (1929) on the pathological aspects of the disease

(1) Age, sex and site incidence

In a consecutive series of 70 patients with laryngeal carcinoma examined by Thomson and Colledge, 30 were in the sixth decade. The mean age of Pack and Le Fevre's series was 57. The mean age of my 11 necropsy cases was 62. New and Hertz saw the disease in a boy of 15. All recorded series show a great predominance of males over females, usually in a ratio of about 10 to 1. The Registrar General's 1931 report showed that fatal carcinoma of the larynx, like that of the mouth and pharynx, showed a decided class gradient amongst males, being highest in the unskilled classes, but, unlife buccal and pharyngeal cancer, laryngeal showed no class gradient in women "suggesting that the factors responsible for the excess of cancer of this site amongst unskilled males are directly associated with occupation".

Intrinsic carcinoma of the larynx arises most commonly in the vocal cords less often in the ventricles or below them. Cancers of the epiglottis, arytenoid region or aryepiglottic folds are uncommon.

(2) Causative factors

Over-use of the voice, syphilis tobacco, alcohol, and various occupational dusts and fumes (references by Hueper) have all been suggested as possible causative factors, but the evidence is mononcluste. Jackson beheved that 65 per cent of laryngeal cancers were preceded by "vocal abuse', but Thomson and Colledge failed to find pre cancerous conditions in most of their cases. The great predominance of the disease in males, and the decided class gradient in males not shared by females, point strongly to occupational factors in causation and inhaled substances may well be the main agents.

Relation of papilloma to carcinoma

Papillary growths of the larynx are of the following kinds (a) Multiple papillomas in children (examples by Bland Sutton Kaufmann, and Ferguson and Scott) numerous cauliflower-like growths spring from the mucosa, and may fill the larynx and cause suffocation Bland Sutton mentioned the spontaneous disappearance of such growths following tracheotomy. Hitz and Oesterlin saw a child in whom multiple bronchial implants developed in the lungs, but mussive carcinoma has not been observed to supervene in this peculiar disease (b) Non invasive but often recurring multiple or single pupillomas in adults, there repeated recurrences some of these show invasive carcinoma (c) Papillary

in the nasopharynx, possessing a rather diffuse structure with lymphoid cells intimately mixed with poorly differentiated earcinomatous tissue. Although Schmincke and Regaud are usually credited as the first to segregate this group of tumours Trotter had clearly described them clinically in 1911, designating them endothelioma. Schmincke's name lympho-epithelioma has been widely adopted the tumours have been divided into Regaud and Schmincke types, and there has been much discussion as to the interrelation-thips of lympho epithelioma', Ewing's transitional cell carcinoma' and squamous cell carcinoma of ordinary structure (see New , Ewing Quick and Cutler', Harvey et al', and Cappell). To add to the confusion some writers e.g. Godifiedsen, group the lympho epitheliomas as sarcomas

In my opinion the controversy is largely over names the various names denote, not distinct entities, but only various of the entity epidermoid carcinoma of the pharmy. The close admixture of lymphoid cells with certain carcinomas arising in the lymphoid areas of the pharvny and throat does not distinguish them sharply from other carcinomas of the region Histologists are still uncertain of the precise relationships of epithelium and lymphoid tissue in the tonsils and thymus-whether the close association of the two tissues means a genetic relationship or an inductive or attractive effect of one on the other. Whatever the interpretation it is not surprising that an association characteristic of the normal tissue of the region should sometimes be perpetuated in its tumours. Moreover, lymphoid infiltration is not peculiar to pharvingeal tumours but is a distinctive feature of some other kinds of tumours e.g. seminoma. From my own examinations of pharyngeal tumours, and from my study of the micro figures in the papers of the various authors already cited especially those of Harvey et al. Cappell and Digby et al. I am satisfied that the lympho epitheliomas are anaplastic earcinomas. that between well cornified squamous cell growths and the most sarcoma like lympho epitheliomas tumours of every gradation of structure can be found. and that a wide range of structure can be found also in some individual tumours (see Fig. 127)

(4) Growth and metastasis

Pharyngeal and tonsillar earcmoma resembles lingual carcinoma in its powers of the wason and metastasis. Direct extension of the nasopharyngeal tumours to the base of the skull often occasions early involvement of one or more of the cranial nerves producing a variety of symptoms and syndromes which have been fully described by New and by Godtfredsen. Dissemination to the upper deep cervical lymph glands occurs early and in a high proportion of cases. Enlarged glands were present in 75 per cent and were the first symptom in 32 per cent, of Codtfredsen's patients. Cervical metastases were present in 24 of my 27 necropsy cases (89 per cent). Many workers have described cases in which large cervical growths secondary to small symptomless tumours of the tonsil or pharynx were mistaken for primary lymph gland or branchial tumours (see below)

Distant blood borne metastases, usually consequent on invasion of the jugular ven from the enveloping cervical growths, are present in about 40 per cent of fatal cases e.g. in 11 of mv 27 necropsies. The organs most frequently affected are lungs, liver, kidneys and bones. Including lymph nodal deposits beyond

In 7 cases the primary sources of the large cervical growths were not discovered during life and in an eighth case the main symptoms had been caused by cerebral metastases of a small pharyngeal carcinoma which was disclosed only by necropsy. The misdiagnoses of the cervical timours included 'branchiogenic carcinoma', 'endothelioma' and lymphosarcoma' of cervical lymph glands. McWhorter, Hudson Graff, Humperl and others have also commented on the frequency of carcinomatous cervical growths of clinically undetermined source, only careful necropsy can reveal the origin of many of these

CARCINOMAS OF BRANCHIAL CYSTS

The foregoing facts show that a clinical or biopsy diagnosis of "branchiogenic carcinoma —a diagnosis usually made merely because no primary source has been discovered—is valueless. Only complete and careful necropsy, to exclude primary tumours in all possible sites can identify a cervical growth as of branchial origin. Cases like those of Lillie et al., Oliver, and many others can be dismissed. My series of 64 necropsies, referred to above, included 2 cases of possible branchial carcinoma. In both cases there were large upper deep cervical epidermoid carcinomas and thorough post-mortem examination failed to reveal any primary growth in the upper alimentary and respiratory passages or elsewhere. Even in these cases, however, the diagnosis is not certain, for the large solid growths had obliterated any evidence there may formerly have been of their origin in cysts and a salvary origin could not be excluded. In the following case the diagnosis of carcinoma of a branchial cyst seems very probable, though again not quite certain

Case II - In 1937 a woman of 25 had had an inflamed left upper cervical swelling incised. Subsequently the swelling fluctuated in size, but began to enlarge steadily early in 1940 In October 1940 the tumour occupying the usual position of a branchial cost was removed. This was a well defined apparently encapsulated ovoid mass 5 centimetres by 3.5 centimetres consisting of firm and friable white growth interspersed by cystic spaces the structure suggesting origin of the growth from the cyst walls Microscopically the growth was a diffuse epidermoid carcinoma mingled with plentiful lymphocytes (Fig 127) Pathological diagnosis carcinoma of a branchial cyst or meta-tatic carcinoma in a lymph gland Careful and repeated examination of the patient failed to disclose any primary growth in the oral nasal or pharyngeal cavities. The patient remuned well until April 1941 when recurrent growth appeared in the neck at the site of the former tumour This steadily extended and finally invaded the floor of the mouth the left tonsillar region and the base of the tongue over a wide area. The patient died in October 1942 at the age of 30. Necrops, showed a large mass of growth in the left side of the neck containing a sloughing cavity continuous with extensive ragged ulceration of the floor of the mouth and tonsillar region Some discrete deposits of growth were present in lymph glands in both sides of the neck. There were no growths in any other organs

The youth and history of this patient, the situation and structure of the initial cervical growth and the prolonged absence of any sign of a primary growth in the oropharyngeal passages, although this was carefully searched for, all support the diagnosis of careinoma in a branchial cyst. There seemed little doubt that the recurrent growth ulcerated only secondarily into the mouth and tonsil region but the possibility that a small undiscovered primary growth in this region may thereby have been submerged cannot be excluded.

carenomas clearly invasive and malignant of milio. In my opinion, no sharp distinction can be made between (b) and (c), papillary growths of the larynx like those of most other sites show a wide range of behaviour and there is no clear line of demarcation between the benign and the malignant. I have seen several cases in which repeated removal of histologically 'benign papillomatous growths has eventually been followed by carenoma and I believe that all papillary growths in the larynx should be looked upon as potentially cancerous

(3) Structure

Almost all larvngeal carcinomas are of the ordinary cornifying epidermoid type adenocar, nomas are very rare Many of the tumours show papillary patterns especially in their early stages. Lympho epithelioma does not occur

(4) Growth and metastasis

Laryngeal carenoma usually grows slowly and metastasizes late. The disease may run a very prolonged course, of 8 or 10 years or longer. The growth, commencing usually on one cord, first spreads horizontally in the eord and often extends across the anterior commission to the opposite cord. Later it may spread in a vertical direction to the base of the epiglottis or to the subglottic area. The laryngeal cartilages act as barriers to the lumour and invasion of the walls of the origan is usually slow. The earliest part to be penetrated is often the anterior part of the crico thyroid membrane.

As long as the tumour remains confined to the interior of the laryns, metastasis seldom occurs but once it has traversed the wall to reach the peri laryngeal tissues metastases often appear promptly in the neighbouring deep cervical lymph glands. The disease often proves fatal however before metastases have developed, deposits were present in lymph glands in only 4 of my 11 necropsy cases. Remote metastases are rare but have been recorded in liver, lungs and other organs

GENERAL SUMMARY OF THE METASTASIS OF EPIDERMOID CARCINOMATA OF THE HEAD AND NECK

In 1930 1934 and 1941 I recorded studies of the necropsy findings in 64 consecutive cases of epiderimoid carcinoma of the facto cervical region. The primary sites were skin in 6 cases, lip 7 tongue 20, tonsil 5 palate 2, pharyax 17, laryax 3 maxiliary antrum 1 alveolus 1 and in 2 cases probably branchial cysts Metastases were present in the cervical lymph glands in 51 cases (80 per cent) Invasion of the main cervical veria, susually the internal jugular vern was found in 30 cases (46 per cent). Remote visceral metastases were found in 25 cases (39 per cent). In all but one of these tumour invasion of cervical veria was present. While in only 6 of the 30 cases with invaded veria were remote metastases absent. These facts clearly show the blood borne origin of these metastases. The organs affected were lungs in 19 cases liver 14 kidneys 8 bones 5, myocardium 4 adrenals 4 thytoid 3 spleen 2 pancreas 2 voluntary muscles 2 and stomach, intestine brain blidder and gall bladder each in one case.

growth, if this has extended widely, conclusive proof of its branchial origin may still be unobtainable even at necropsy

EPIDER MOID CARCINOMAS OF THE OROPHARYNGEAL REGION IN ANIMALS

Feldman gives references to scattered records of oral, pharyngeal or larvageal carcinoma in the horse dog cat, wolf, bear and fowl. The most frequent of these were careinomas of the gums in horses, and of the tonsil or pharynx in does Of 67 careinomas of dogs studied by Rudduck and mc, 12 were epidermoid carcinomas of the oral cavity arising in the gums in 2 cases and in the tonsils in 10 cases we reported two of the tonsillar tumours in 1938. Withers also has described carcinoma of the tonsil in the dog. Like its human counterpart, this tumour is prone to produce large metastatic growths in the cervical lymph glands while the primary tumour remains small. Steiner et al reviewed the lew recorded cases of carcinoma of the tongue in animals, and added two examples of this disease in monkeys

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I have yet to see a completely acceptable case of branchiogenic carcinoma, or indeed a completely acceptable report of such a case While it is very probable

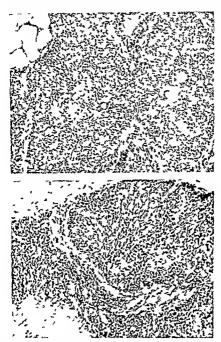


Fig. 127—Care II Caremoma of lympho-epithelial type probably arising in a branchial cyst. Note diffuse structure, patchy incomplete carnification and admixture of lymphocytes. (× 120)

that this tumour does occasionally occur it is certain that the great majority of tumours so designated are metastases from undetected primary growths elsewhere Furthermore as Case II just described shows even in a case of genuine branchial

CHAPTER 16

TUMOURS DERIVED FROM THE EPITHELIUM OF THE DENTAL LAMINA

THE DEVELOPMENT OF THE DENTAL LAMINA AND TOOTH GERMS

A knowledge of the development and fate of different parts of the dental lamina is essential to an understanding of the origin of the epithelial tumous and tumour-like malformations of the raws

A tooth is a compound structure derived from two distinct embryonic tissues. The enamel cap of the tooth is an epithelial derivative of the dental lamina, which grows from the lining of the embryonic buecal cavity into the substance of the jaw. All other parts of the tooth—dentine, cementum and pulp—are derived.



Fig. 128—Vertical section through a tooth germ of a 15 weeks foetus showing oral mucosi (0) dental lamina (D) and enamel organ (E) with stellate reticulum (× 60)

from the embryone mesenchyme. The outgrowth of the dental lamma corn mences in the fifth week, as it extends into the mesenchyme of the jaw, it develops two successive series of bud like the kenings the first rudiments of the deciduous and permanent teeth. Each epithelial tooth germ or 'enamel organ' enlarges grows deeper into the jaw and its attachment to the dental lamma becomes constricted. At the same time its deep surface becomes indented by a condensed mass of mesenchyme so that the enamel organ is now bell shaped, forming a thick epithelial cap over the papilla [Fig. 128]. This cap consists of three zones—(i) the internal enamel epithelium—a layer of tall columnar cells or anuloblasis.

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are visible in the dentine of a growing tooth, an increasingly wide calcified zone and a narrow uncalcified zone adjacent to the layer of odontoblasts. As the dentine increases in thickness, the odontoblasts recede, and finally attain their permanent position around the periphery of the connective tissue pulp. A thin layer of bony tissue or cementum later develops on the outer surface of the root dentine, at the neck of the tooth there is a junction of cementum and enamel. These relationships are of interest in interpreting the structure of the odontomes Study of these growths confirms the impression, gained from embryological research, that the formation of odontoblasts and dentine is dependent on the presence of enamel-organ epithelium (see Mummery, and Hutley and De Beer)

In Chapter 1 it was pointed out that, in tissues the histo differentiation of which is not completed before birth, tumour-like malformations may result from post natal disturbances of growth. This is particularly relevant for the tooth formative tissues, adulthood of which is not attained until eruption of the permanent teeth is complete. The epithelial residues of the enamel organ and of the dental lamina, are plentiful around uncrupted teeth, and may help to determine the direction of cruption (Mummery), inflammatory or nutritional disturbances may readily be conceived to induce proliferative changes or cyst formation in these residues during childhood or adolescence. So also in the young growing tooth in which active formation is still in progress, local infective or other disturbances may well evoke overgrowth or dislocation of cnamel, dentine or cementum. These theoretical deductions are supported by study of the structure of odontomes, cysts and 'adamantinomas', and especially by the fact that most of these abnormalities appear early in life

CLASSIFICATION AND ORIGIN OF DENTAL EPITHELIAL TUMOURS

As in so many other special fields of pathology, there has been needless elaboration of the classification and naming of the malformations, cysts and tumours connected with the tooth formative tissues. In my opinion, the only essential subdivisions of all of these lesions are the following

- (a) 'Adamantinoma' or ameloblastoma' is a true neoplasm derived from the epithelial residues of the enamel organ', the developing tissues of which the tumour structurally resembles The old name 'epithelial odontome' is fortunately almost obsolete this tumour is unrelated to the odontomes proper The current names, 'adaman timoma' and "ameloblastoma', are also misnomers, for the tumours do not arise from ameloblasts and do not form enamel (see below)
- (b) Intra alveolar epidermoid carcinoma is carcinoma of the ordinary squamous cell type, unconnected with the epithelium of the gums and arising in the substance of the jaw. Its origin must be from the paradental epithelial residues, and in view of its structure and its distinction from adamantinoma, we may suspect its source to be squamous-cell residues of the dental lamina rather than the residues of the tooth-germs.
- (c) Odontomes are benign tumour like malformations in which varying mixtures of tooth tissues proper—enamel, dentine and cementum—

in contact with the papilla (ii) the external enamel epithelium a superficial layer of small cubordal cells on the convex aspect of the enamel organ and (iii) an intervening zone of shrunken epithelial cells connected only by long processes and elsewhere separated by clear intercellular fluid, forming the stellate reticulum or enamel pulp. Only the first of these zones, the layer of ameloblasts, will produce v

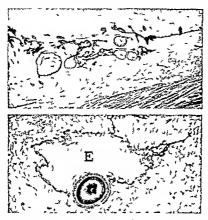


Fig. 129 (a) and (b) —Horizontal sections through jaw of a 6-months focus: (a) at a plane just beneath the gam to show epithelial remains of the dental lamina including cormified pearls (b) at a plane through the summit of a tooth to show the great amount of non-enamel formative epithelial returding (F) around the tooth (× 40)

the enamel of the developed tooth the remainder of the enamel organ at this stage by far its bulkest part will not form enamel but will persit as the para dental epithelial residues or sheath of Hertwey in the percodontal membrane around the fully formed tooth. Epithelial residues of the dental lamina itself also persist in the connective tissues around the sumants of the developing teeth partly in the form of rounded cornified islands or epithelial pearls (Fig. 129) these are visible in infants as nodules under the gums the so called 'glands of Serres. It is from these various epithelial residues that epithelial tumours and cysts within the laws arise.

The dentine of the developing tooth is produced by a layer of specialized mesenchymal cells the odontoblasts which arise it the periphery of the dential appilla adjacent to the ameloblasts. The dentine appears between the ameloblasts and the odontoblasts as a layer which gradually theckers. Two distinct zones

are visible in the dentine of a growing tooth, an increasingly wide calcified zone and a narrow uncalcified zone adjacent to the layer of odontoblasts. As the dentine increases in thickness, the odontoblasts recede, and finally attain their permanent position around the periphery of the connective tissue pulp. A thin layer of bony tissue or cementum later develops on the outer surface of the root dentine, at the neck of the tooth there is a junction of cementum and enamel. These relationships are of interest in interpreting the structure of the odontomes. Study of these growths confirms the impression, gained from embryological research, that the formation of odontoblasts and dentine is dependent on the presence of enamel organ epithelium (see Mummery, and Huvley and De Beer)

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are present. These tissues are usually disorderly in arrangement and do not form properly developed teeth, though teeth may be associated with or incorporated in them.

(d) Epithelium lined c) sts in the jaws are formed in several different ways and of course are not true tumours. Some of them represent disturb ances of eruption or other developmental malformations and such eysts are often demonstrably connected with malformed or malerupted teeth or they may contain supernumerary teeth or denticles. Others, like the simple dental cysts attached to the roots of dead or diseased. teeth are related to root granulomas in which plentiful epithelial tissue is often present associated with the inflamed granulation tissue This epithelium is derived from the paradental residues around the roots and epithelium lined root-cysts clearly arise from it so called radicular odontomes -abnormal masses of dentine and cementum attached to the roots of teeth-are related to the root cysts and granulomas As Bland Sutton said Many radicular adoptomes are probably due to inflammatory changes affecting the roots of incompletely developed teeth. Cysts and root granulomas will not be considered further here

ADAMANTINOMA OR AMELORIASTOMA

The tumours of the jaws designated by these names are lowly malignant slowly growing epithelial tumours of rather characteristic microscopical structure which closely resembles that of the developing enamel organ but which do not form enamel Good accounts include those of Simmons (1928) Robinson (1937) Ringertz (1938) and Thoma and Goldman (1946), and the following personally studied cases are illustrative of the group

Case I—A man aged 43 complained of steady enlargement of the right half of the mandible for 2 years commencing near the first molar text. Examination showed great enlargement and expansion of the bone by a tumour 8 contimetres in diameter extending from near the angle to within 2 contimetres of the symplysis externally forming a smooth rounded swelling internally a lobulated mass with impending ulceration of the mucous membrane Excision of the right half of the mandible along with the involved mucous membrane was performed with good recovery. Examination of the timour verified its extent and showed firm whitish tumour tissue constaining many small cysts. Microscopically this showed masses of epithelial growth partly resembling basal-cell cureinoma of the skin partly resembling enamed organ epithelium and both sold and cystic (Figs. 130 and 131).

Case II—Early in 1929 a woman aged 22 complained of swelling of the left side of the mandible for the previous 18 months following tooth extractions. Operation disclosed a polycystic dental cyst which was curetted out. The swelling reappeared during 1930 and increased until June 1931 when operation disclosed polycystic growth which was curetted out and radium inserted. Microtocopical examination showed cystic adamantinoona. Deep X-ray therapy was applied during the next 3 years but the tumour slowly recurred. In August 1935 conservative operative removal of the affected area of bone was performed, and microscopical examination again showed cystic adamantinoona. Further slow recurrence took place and was again treated by local removal, this time with success the patient remained free of the diseases in 1931.

Case III — In 1932 a woman aged 29 noticed a swelling diagnosed dental cyst near the left angle of the mandible. This was removed surgically in 1934. At the end of 1938 a recurrent mass of growth was removed microscopical examination showed

cystic adamantinoma. The tumour rapidly recurred, and in March 1940 it presented as a large lobulated mass projecting into the mouth and extending up into the temporal fossa and down into the neck. About 60 grammes of tumour tissue were removed by curettage, this again showed cystic adimantinoma (Fig. 132). The patient died in 1941 from extensive recurrence, and supervients infection.

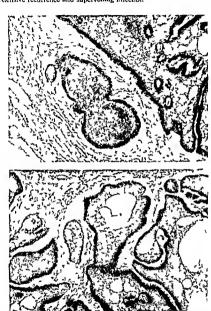


Fig 130(a) and (b)—Case I Adamantinoma (a) shows solid tumour clumps resembling those of basal cell growths of the skin and containing small squamous cell foci and (b) shows cystic change in stellate reticulum (x 50)

Case IV—A man aged 49 complained of slight swelling of the molar region of the right side of the mandible for 18 months past previous to which he had pulled out a Roose tooth the socket of which then failed to heal Operation disclosed a loculated cycle full of granulation tissue which was curetted out Microscopical examination and with the manufacture of the molar region of the roots which was curetted out Microscopical examination and which was curetted out Microscopical examination and which was curetted out Microscopical examination.

Ca re V-Necropsy on a man aged 67 who had complained of enlargement of the mandly ble for 2 years showed an extensive solid growth replacing the left half of the boat and und erating into the floor of the mouth but without metastases Microscopical

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(2) Structure

Typically adamantinomatous" epithelium, depicted in Figs 130 132, consists of well defined clumps with rounded or angulated contours, the marginal cells of which are of tall columnar form with their nuclei away from their bases, and the central cells of which form in open meshwork with many intercellus spaces closely resembling the stellate reticulum of the developing cnamel organ Accumulation of fluid in the intercellular spaces in the cpithelium frequently produces small or large cysts, which give a honeycombed or pseudo glandular appearance

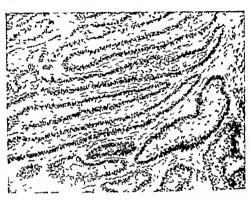


Fig. 132—Case III Typical though elongated adamantinoma clumps showing the internal (i.e. non basal) position of the nuclei of the marginal cells (× 80)

Other parts of the tumours may show little or no stellate reticulum, and the structure may closely resemble that of basal cell careinoma of the skin, especially of the cystic type (Fig 130A) Epidermoid characters also may be present, including spinous cells small cornified foci, or well formed squamous cell parls If epidermoid structure is prominent, distinction from epidermoid carcinoma of the jaw is scarcely possible (see Case V) All structural variants may be found in one tumour Mitotic figures in the tumour cells are few Old areas of growth often show gross cystic changes haemorrhage or patchy calcification Unerupted teeth or fragments of bone are sometimes found incorporated in the tumours

(3) Growth and metastasis

Though usually of slow growth the tumours distend invade and destroy the surrounding bone, and, unless wide excision is carried out, post operative recurrence is frequent. Attempts to distinguish benign and "malignant"

examination showed carcinoma partly of cormfying squamous type but with areas showing stellate retrudar structure in the epithelium. The tumour was provisionally called adamantinoma but it could equally well have been called epidermoid carcinoma with adamantinoma like structure.

Case VI (Case XI of Chapter 18) -A woman aged 46 with enlarging tumour of left maxillary antrum for 4 years

(1) Age, sex, race and site incidence

In a review of 379 recorded cases, Robinson found that the average age when the tumours were first noticed was 30 years and that 70 per cent of them appeared

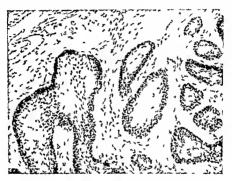


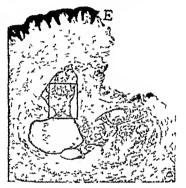
Fig 131 -Case I Typical adamantinoma clumps (x 100)

between the ages of 10 and 35 years. They may appear in childhood or infancy. Euler saw one in a child aged 13 months and referred to another proven case at 6 months. They rarely appear over the age of 50 years. Many of them are of slow growth and long duration even as long as 40 or 50 years but more rapidly growing tumours (like my Case I) are not unusual. Untreated tumours may attain huge sizes, even as much as 1 500 grammers.

The sexes are about equally affected 54 per cent of the cases reviewed by Robinson were females The disease occurs in Negroes Chinese and Indians Adamantinomas occur more frequently in the lower than in the upper jaw—in 84 per cent of the cases reviewed by Robinson and in the same percentage of Geschickter's cases This difference may however be partly fictitious since some at least of the maxillary adamantinomas escape recognition as such and are classed as adenoid or basal-celled growths of the antrum or nasal cavity (see Chapter 18)

supported by the following very early case of subgingival epidermoid carcinoma

Case VII—A woman aged 60 had recently noticed a small firm well defined nodule on her lower molar gum margin beneath her dental plate. This measured about 4 millimetres in diameter and was clothed by intact healthy mucosa. Microscopical examination after excission (Figs. 133 and 134) showed it to be a circumscribed epidermoid carcinoma with plentfull cornification and some small cysts in the epithelial masses.





Figs 133 and 134—Case V/I Early squamous-cell growth of subgingival epithelial residues
E = epithelium of gum (x 15 and 120)

adamantinomas are futile, they are all malignant in that they are locally invasive and prone to recur. Metastasis to the cervical lymph glands or lungs is infrequent, but has occurred in a few cases e.g. in those of Ewing, Simmons (Cases 2 and 7) and Vorzimer and Perla. Vorzimer and Perla is case showed unique intrabronchial metastasis evidently due to inhalation of tumour fragments from the advanced maxillary adamantinoma which had invaded the nasal cavity and pharynx.

(4) Comment on histogenesis

The frequently unmistakable resemblance of adamantinoma to enamel organ epithelium points to this tissue as the origin of the growth. The failure of the tumour to form enamel though perplexing to those who accept the names adamantinoma and ameloblastoma at their face value, accords with the developmental history of the tooth germ epithelium. The only part of this estimated to form enamel is the internal enamel epithelium or layer of ameloblasts external epithelium and stellate reticulum form no enamel either in normal development or in tumours. To call these tumours by either of the prevalent names is therefore erroneous at would be better to call them carcinomas of the tooth germ residues.

It is relevant to mention here the so called adamantinomas of extra oral sites the pituitary region and the tibia. The dental lamina arises as an outgrowth of the embryonic oral ectoderm and leaves epithelial residues around its special derivatives the teeth so also Rathke's pouch arises as an outgrowth of the same oral ectoderm and leaves epithelial residues around its special derivatives the epithelial parts of the pituitary gland. It is then not difficult to understand why these two groups of indifferent epithelial residues should give origin to tumours of similar structure and with a similar incidence at relatively early ages. Further, the adamantinomas of the pituitary region clearly have no histogenetic relationship to any enamel forming epithelium—a further reason for recognizing this name as a misnomer. The so called adamantinomas of the tibia (Chapter 14) are bone invading epidermal carenomas parts of which sometimes show some structural resemblance to the oral and pituitary adamantinomas but of course occasional resemblance is not identity. Even ordinary squamous cell carenoman got the shin occasionally resembles adamantinoma (Fig. 93)

INTRA ALVEOLAR EPIDERMOID CARCINOMA

Rarely a squamous cell carcinoma of ordinary structure and behaviour arises in the substance of the jaw widely invades and destroys the bone and may ulcerate secondarily into the mouth. Thave performed necropsies on two such cases, one in a woman aged 63 years and the other in a woman aged 63 both with metastases in the cervical lymph glands. Case V above might also be placed in this group. The number of recorded tumours of this kind is too few for analysis of their properties but most of them have appeared in elderly people and have shown a degree of malignancy like that of oral epidermoid carcinoma in general. In spite of tumours of borderline structure, like Case V the group on the whole is distinct from the adamantinomas suggesting a different origin doubless the squamous celled residues of the dental lamina (Fig. 129). This origin is

fully formed dentine and enamel related to each other as in normal tooth development but with disordered arrangement, including, as in Pritchard's specimen reversed position of dentine and enamel

Horbst's case, a girl of 9 years, provided a good example of the rare soft odontomes, containing young tooth germs with embryonic connective tissue clothed by epithelium, but without fully formed dentine or enamel Such odontomes with immature tissues have sometimes been called "adamantinomas". but as Euler insisted, the two can and should be distinguished

Mummery and Pitts reported a unique odontome removed from the incisor region of an infant, in addition to dental tissues, this growth contained melanotic epithelial tissue. Its benign character was attested both by its encapsulation and the fact that there was no recurrence 4 years after its removal. Although described as an "epithelial odontome" and included by Robinson in his review of ameloblastomas, this tumour must be classed with the odontomes proper

TUMOURS OF DENTAL TISSUES IN ANIMALS

In most cases, dental "tumours" in animals are not true neoplasms but eystic malformations or odontomes

These have been seen in great number and variety in most species of domesticated animals and in many wild species also, Colyer has fully described and depicted many examples Bullock and Curtis observed odontomes in rats, and Zegarelli in mice

Adamantinomas comparable with the human tumours have rarely been reported from animals Zegarelli described as "adamantoblastoma" 103 solid or cystic growths in the jaws of mice, some of which appear clearly to have been true tumours mainly of squamous cell type, while others were non neoplastic odontomes Nieberle and Cohrs stated that adamantinomas occur in the ox and eat, and Ratcliffe that he had seen one example in a rat, but no details are given The tumour described by Orr as "adamantinoma' in a rabbit was a squamous cell growth associated with cysts lined by ordinary squamous stratified enthelium

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The tumour diagnosed by Orr (1936) as adamantinoma '' in a rabbit was a cystic squamous cell growth

ODONTOMES

It is questionable whether the odontomes are neoplasms. Many of them pare known to have been present since infancy or childhood, and to have enlarged only pair passu with the growth of the rest of the dental tissues or as the result of secondary infection and inflammation. In these respects they behave rather like mailformations than like true tumours. I propose therefore to devote little space to them but to refer the reader to the naked eye descriptions of Bland-Suiton (who gave earlier references), and to the detailed histological studies of Rywkind Pritchard Euler, Horbst, and Thoma and Goldman. These show clearly the disorderly arrangement of the tissues in adontomes the presence of tissues at all stages of formation, the dependence of dentine formation on the presence of epithelium and the frequent reversal of position of these two tissues, enamel and enamel organ epithelium often being found centrally situated within masses of dentine.

The following is an example of an old fully mature quiescent odontome

Case HII —A man aged 47 years had had a swelling of his maxilla for many years this had remained unchanged until an adjacent tooth had been extracted since when the mass had been tender and a small discharging sinus had persisted. At operation a well defined irregularly rounded mass 2 centimetres in diameter situated in the right maxilla in the lateral incisor and canne region was removed. Serial sections after decalerification showed it to be a conglomeration of denticles or tooth like masses consisting mainly of dentine clothed here and there by a layer of ename of very irregular distribution and thickness. I jung between the better formed denticles there were also smaller irregular pieces of dentine many of which showed vacuolation and spherical cakified bodies. The soft tissue intervening between the tooth tissues was largely inflamed granulation tissue in which however there were existenced groups of epithelial cells.

Pritchard summarized his well illustrated account of an odontome in a boy of 7 years as follows. This tumour started at a very early age in the backward growth of the tooth band distal to the first molar, in that part of it destined for the formation of the second and third molar teeth. It consisted at first of branching columns of columnar epithelium which burrowed in the embryonic connective tissue in the interior of the mandible. As it grew it determined the formation of dentine which subsequently calcified in contact with it enamel calcifying approximately simultaneously. As the dentine formid neighbouring masses coalesced or tended to do so, to surround or enfold columns of enamel. The connective tissue more remote from the growing epithelium tended to reach maturity and form fibrous tissue which in the end would have become the fibrous capsule of the mass. At or after this stage cementum deposition would have become possible. As in the case of a tooth when the enamel organ and Hertwigs sheath have completed their primary function of shaping the tooth, and in the former instance also of forming enamel, epithelial growth stops. So in the case of such an odontome would growth ease at the end of formation and calcification.

Rywkind's excellent study of an odontome in a girl of 8 years showed all stages in the formation of dental tissues from early tooth germ tissue up to

CHAPTER 17

EPITHELIAL TUMOURS OF THE SALIVARY GLANDS

Many of the earlier writers on salivary tumours sharply distinguished the rare adenomas and carcinomas from the much larger group of so called "mixed" tumours. This distinction, we may now recognize, was an artificial one, for, as will be shown the mixed tumours" are adenomas and lowly malignant adenocarcinomas, with a wide range of structure and behaviour, and they merge insensibly with the simple adenomas on the one hand and with the frankly malignant anaplastic carcinomas on the other. Hence, while it is convenient for descriptive purposes to continue to use these names it is essential to understand that they denote, not distinct classes of tumours but merely variants of a single histogenetic group. With this clearly in mind and adding the distinctive group of rare adeno-lymphomas we shall discuss the salivary epithelial tumours under the following main heads

- (a) Simple adenomas
- (b) Pleomorphic adenomas and adenocarcinomas (so called 'mixed"
- (c) Anaplastic carcinomas
- (d) Adeno lymphomas

SIMPLE SALIVARY ADENOMAS

A few salivary tumours are so uniform in structure and composed of epithelial tissue so unmistakably like that of the salivary glands, that their simple epithelial character has always been admitted, and accordingly they have been separated from the supposedly 'mixed'" tumours under the quite correct caption of "adenoms.'

However, the view already expressed that this separation is artificial, rests on the following grounds (a) Areas of simple adenomatous tissue resembling that of the simple adenomas are to be found in the 'mixed' tumours (b) Otherwise typical salivary adenomas may show in minor degree some of the structural characters of the 'mixed' tumours thus Ewing said 'several authors have described transitions to myxo chondro carcinoma', Fry concluded that on structural grounds no sharp line can be drawn between adenomas and mixed tumours, and Harvey et al in their Fig 16 depicted a densely eneapsu

mixed tumours, and Harvey et al in their Fig 16 depicted a densery challed tumour of pure adenomatous type with a mucoid stroma (c) If the supposedly mixed" tumours are, as will be shown not mixed but are purely epithelial growths arising from salivary glandular tissue then clearly there can be no sharp distinction between these and the simple adenomas for they are of identical origin. The adenomas are then only a variant of the whole group, namely the most slowly growing and innocuous variety with a uniformly differentiated structure.

Typical examples of adenomas were described by Schutz Steinhardt, and Škorpil, and Eggers classified 2 of his 7 palatal tumours as adenomas Schutz

Orr J W (1936) J Path Bact 42 703

PRITCHARD G B (1932) The origin and growth of a composite adontome Proc Roy Soc Med , 26 472 (A valuable well illustrated study)

Ratchiffe H L (1940) Amer J Path 16 237

Ringertz, N (1938) Reference Chapter 18 Robinson H B G (1937) Arch Path 23 664

ROBINSON H B G (1937) Amelobiastoma A survey of 379 cases from the literature . Arch Path 23 831

RYWAIND, A W (1930) Zur Pathologie der Odontome Vuchous Arch 277 228 (An excellent account with beautiful illustrations i

Simmons C C (1928) Ann Surg 88 693
THOMA, k H and GOLDMAN, H M (1946) Odontogenic tumors Amer J Path, 22 433 (Good illustrations show well the range of structure in the tumours and adontomes) Vorzimer J and Perla D (1932) Amer J Path 8 445

ZEGARELLI, E. V. (1944) Adamantoblastomas in the Sive stock of mice. Amer. J. Path. 20 23 (A well illustrated account of odontomes and dental enithelial tumours)

of cells already in an advanced state of differentiation." Ewing (1940), while appearing at first to support the epithelial salivary origin of the tumours, then supposed that, 'No single source of the mixed tumors meets all the requirements', that some of the tumours "probably arise from misplaced, and occasionally, embryonal portions of gland tissue', and that "branchial remnants may possibly be connected with this group." So also, Kaufmann (1929) after expressing adherence to "the epithelial theory", qualified this by adding 'that an endothelial derivation is possible exceptionally. Ahlbom in his monograph (1935) gives much useful information about salivary tumours, but vacillates over their histogenesis and speaks of "chondroma", "fibro myxo epithelioma' et

Thus in the works of recent and authoritative writers, we find views expressed which show that none of the old notions is quite extinct—Cohnbeim's embryome cell rests, branchial enclavement, endothelial origin, are all represented

Many of those workers who have argued for the essentially epithelial salivary origin of the tumours, have nevertheless accepted without question the prevalent belief that they contain "cartilage", and have devised various explanations of the origin of this cartilage". Usually they have then continued to speak of mixed" tumours explaining the "cartilage" as a product of metaplasia in the stroma (e.g. Muir, 1941) or by concluding that true cartilage may arise by direct transformation of the epithelium itself. Thus according to Ewing the derivation of mucous tissue and cartilage from gland epithelium has been salis factorily proved.

In what follows I shall present briefly the evidence which fully convinces me that, (a) these tumours are not "mixed" but arise from and consist of salvary epithelial tissue only, (b) with very rare exceptions, they contain no mucous connective tissue and no cartilage, and (c) in those rare tumours in which cartilage (or bone) is present this is quite different from the supposed "cartilage so common in the tumours and has clearly arisen by metaplasia in the connective tissue stroma just as may occasionally happen in many other kinds of tumours I must say also that, granted some justification for the conflicting views of the earlier explorers of this field, I find myself unable to comprehend how any modern histopathologist after studying the structure of these growths with reasonable care, could possibly come to any other conclusions than the foregoing

Some workers, though satisfied of the simple epithelial nature of the tumours have retained the term 'mixed' as appropriately denoting the variety of structure in the growths. Because of the erroneous connotation of the term, however I prefer to discard it in favour of the purely descriptive adjective "pleomorphic

(2) Age incidence

These tumours arise at all ages from early childhood onwards greatest number make their appearance in the third and fourth decades (Wishon and Willis, McFarland) More than one half of the tumours appear duming these two decades, between which they are distributed about equally Two thirds of the tumours begin before the age of 40 and nearly seven eights of them before the age of 50 Their first appearance in old people is quite rate. They are not unusual in childhood and early adolescence, e.g. at 15 (Harvey et al.), 10 (Fry), and 9 years (Chevassu, Zymbal), and occasionally they are

insisted that a diagnosis of admoma can only be made after thorough examination of all parts of a growth since a tumour the bulk of which is adenomations may show small areas of myted? structure. The pure adenomas are slowly growing encapsulated tumours composed of lobular masses of epithelial tissue which may be partly of acinar structure but may be largely solid and devoid of furning. Acinar cavities in adenomas may contain mucoid secretion.

PLEOMORPHIC SALIVARY ADENOMAS AND ADENOCARCINOMAS (SO CALLED MIXED TUMOURS)

(1) The confusion of ideas and names

About nine tenths of all salivary tumours fall in this group, commonly designated mixed tumours. The term mixed a misiomer when applied to the growths themselves is an apt enough description of the many conflicting and ill founded views which have been expressed regarding their histogenesis. In 1909 Fick was able to say. On the interpretation of mixed tumours scarcely two authors agree on all points and while an intereasing number of competent pathologists (e.g. Fick. Krompecher Bottner Fry Patev Zymbal Harvey et al.) have become convinced of the pure epithelial nature of these tumours we are still far from unanimity.

It would serve no useful purpose to review in detail the bewildering welter of hypotheses regarding the mixed tumours for most of them lack any real basis and they have been adequately outlined by Wood krompecher, Bottner Chevassu Ahlbom and others Suffice it to say that these tumours have been called sarroma endothelioma mesothelioma chondroma

cylindroma adeno chondroma chondro carcinoma branchioma' enclavoma progonoma turatoma and teratoblastoma as well as such hyphenated monstrosities as fibro myxo endothelioma, adeno myxo chondro sarcoma and chondro myxo haemangio-endothelio sarcoma! This chaos of names (surely a warning for would be nominiciators) is indication enough of the diversity of ill founded views which have been held regarding the nature of these timpours

These names and views would be only of antiquarian interest did not some quite recent authorities still cling to part or whole of some of the erroneous notions implied in them. Thus McFarland (1926) insists that the tumours do not arise from salivary tissue and thinks that enclavement of embryonic cells affords the best explanation of their origin. He says. Mixed tumors are individual entities having no relation to the normal structures in which they occur but from which they do not arise. They have nothing to do with other kinds of tumors and should be called. mixed tumors' and nothing else regardless of their histology. McFarland expressed similar views in his. Surgical Pathology. (1924) and did not indicate any afteration of them in his recently published paper (1942). Kux. (1931) and Hempleman and Womack. (1942) upheld the view that they are 'truly mixed tumors' related in their origin to embryonic alteration in tissue relationships. MacCallum (1940) thought. most acceptable and credible' the view that these tumours' represent the teratomic derived from the isolation.

The relative frequencies of tumours in these various sites may be judged from the accompanying Table, which includes only tumours of clearly specified situations.

TARIF

| | | | | Parotid | Submaxillary | Sublingual | Palate | Lips and other sites | Total | |
|--------------|-----|---|---|---------|--------------|------------|--------|----------------------|-------|--|
| Patey - | ~ | ~ | ~ | 38 | 6 | | 5 | 5 | 54 | |
| Zymbal - | -, | | - | 55 | 2 | | | 1 | 58 | |
| Harvey et al | ~ | - | _ | 230 | 21 | 2 ' | 6 | , 9 | 268 | |
| Willis ~ | - | - | - | 35 | 6 | , 1 | 5 | 1 | 48 | |
| Totals | ~ | _ | _ | 358 | 35 | 3 | 16 | 16 | 428 | |
| Percenta | ges | - | - | 83 | 8 | 1 | 4 | 4 | 100 | |

McFarland s large series (1942) is not given in this table because he considered only tumours of the three major glands—these comprised 380 from the parolid 12 from the submaxillary and 2 from the sublingual gland, though McFarland admitted that the proportion of submaxillary tumours in his series might be under-estimated—Submaxillary tumours are specially considered by Chevassi, and by Dockerty and Mayo, and palatil tumours by Eggers d Aunoy, Davis and Stobie

The Table shows that, approximately, for every 100 parotid tumours, there are likely to be seen about 10 submyatillary tumours, 10 tumours of the maor salivary glands (of which about half will be palatal), and only one sublingual tumour. These estimates agree almost exactly with those of Bohme (cited by Wood), who found parotid tumours to be ten times as frequent as submavillary tumours and sublingual tumours to comprise one per cent of the total the three glands, the approximate average weights of which are parotid 25 grammes, submaxillary 8 grammes, and sublingual 3 grammes. We must also postulate differences in the susceptibility of the respective tissues to neoplate and the submaxillary gland contains a higher proportion of these than the sublingual gland, it may be that the serous or albuminous type of cell is more prone to neoplassa than the mucous type. We shall see later whether or not histogenetic studies support this supposition.

A final point regarding the situation of the tumours with respect to the affected glands requires comment. While in most cases the tumour quite clearly lies within the gland, several workers have observed tumours contiguous with but separate from the pirotid or submaxillary glands and this fact has been used as an argument in favour of an origin extrinsic to salivary tissue, e.g. from branchial remains. The unsoundness of this argument will be obvious to anyone familiar with the anatomy of the salivary glands outlying lobules or tubules of which especially of the parotid are often to be found in the surrounding tissues, or included within neighbouring lymph glands (Nicholson)

seen in infants e.g. in Schilling's case a parotid tumour removed from a man of 41 years had been present since the age of one year and in one of Wood's cases a parotid tumour was noticed soon after birth and was removed at the age of seven month. Of 380 cases collected by McFarland 8 occurred in the first decade of life. In my own series the lowest recorded age was 14 years, while another tumour subsequently fatal from metastases at the age of 29 had first appeared at the age of 16 McFarland (1936) shows that the age of appearance of the tumours has no bearing on their degree of innocence or malignancy. The ages at the time of first operation are on an average about 6 years later than the ages when the tumours first appeared. In my own series the ages at operation were as follow.

| | | | | | 1 | | | T | | - | | | | | |
|-------------|---|---|---|---|---|---|----|---|---|---|---|---|---|---|------------|
| Decade - | - | i | ţ | 2 | 3 | ŀ | 4 | ì | 5 | ļ | 6 | 7 | 1 | 8 | |
| No of cases | - | 0 | 1 | 2 | 8 | | 12 | 1 | 6 | 1 | 5 | 6 | | 0 | ≈ 39 cases |

Average age at time of operation 38 years

(3) Sex incidence

Although there is but little difference between the sexes in their liability to salivary tumours many of the recorded series show a predominance of females Thus Bottner's 25 cases comprised 15 femiles and 10 males. Fry s 25 cases 14 females and 11 males, McFarland's 396 cases 212 females and 184 males and in my own series of 50 cases of known sex, there were 34 females and 16 males Some series, however, have not shown an excess of females e.g. Chevassu s study of 57 tumours of the submaxiliary gland comprised 30 males and 27 females, and of the 56 mixed salivary tumours of Wilson and Willis s series 30 were in males and 26 in females

(4) Race and species incidence

There are no reliable comparative statistics That all the main European peoples are liable to salivary tuntours is shown by the plentiful cases in English French, German Italian and Russian reports Amenican records contain in addition references to salivary tumours in negroes and they occur also in the Chinese (Balme Yen Davis) and Hindus (Street)

Harvey and co authors briefly mention five mixed salivary tumours in dogs

(5) Site

The parotid is much more frequently affected than the other salivary glands but similar tumours arise from salivary glandular tissue wherever situated not only from the three pairs of large glands but also from the small glands which are widely distributed around the oral cavity in the lips cheeks palate and floor of the mouth

(7) The structure of the tumour parenchyma

By far the best account of the microscopical structure of salivary tumours is that of Zymbal of Leningrad (1933), whose beautifully illustrated paper is a model of scientific clarity. Anyone who can read Zymbal's paper and still doubt the simple epithelial nature and origin of the so called "mixed" tumours is pathologically incorrigible. Other commendable accounts are those of Patey (1931), Fry (1928), and Harvey and co authors (1938). The following outline, which is based on my own series of specimens, accords with the descriptions of these workers.

The structure of the tumours is very variable, in some tumours many or all of the possible variations of structure may be found in close juxtaposition with all gradations between them, in other tumours one or another structural variant predominates. The following types of structure may be described in tum

- (a) Nearly normal looking salivary tissues
- (b) Atypical glandular tissue
- (c) Atypical glandular tissue with marginal epithelial sprouting
- (d) Solid epithelial formations
- (e) Epithelial formations with cystic spaces
- (f) Cornifying stratified epithelial structures
- (g) Epithelial filaments and networks in a mucinous matrix
- (h) The so-called ' cartilage like" tissue
- (1) Areas with frankly carcinomatous characters

(a) Nearly normal looking salivary tissues

Many of the tumours contain actuar and duct like structures which, divorced from the atypical tissues with which they are mingled, closely resemble the acini and ducts of normal salivary tissue. The most typical acini are to be seen in regions where, as will be described later, there is a direct transition of salivary tissue into tumour In these situations as Fry has pointed out and I can confirm (see Figs 142-144), typical salivary acini still with zymogen or secretory granules in the cells constitute part of the growth. Although glandillar acmi deeper in the growths show no typical granules in the cells, they are often unmistakably like salivary acini in other respects, both as regards their general arrangement with respect to duct like structures and their cytology Instead of containing darkly stained secretion granules, the cytoplasm usually appears finely foamy or vacuolated as though secretory material had been dissolved out. As regards duct like structures in the tumours, Fry, Harvey et al and others have pointed out the frequent presence of elongated or branching tubules lined by a double layer of epithelial cells resembling or identical with those of normal salivary ducts From my own specimens I can confirm this to be a very common feature From the findings in Case I, above, and Case III, to be described, as well as from the general relationship of these tubules to lobular clusters of tumour acini in some of the growths, I strongly suspect that some at least of these tubules are not merely duct like structures formed as the tumour grows, but actually salivary ducts which have participated in the neoplastic change along with their attached lobiles of acini

(6) Relation to antecedent disease

With few exceptions, the subjects of salivary tumours give no history of antecedent disease of the glands—and there is no positive evidence that mumps—suppurative parotitis, salivary calculu or trauma predispose to tumour formation. However information on these points is rarely recorded in hospital histories, and there is room for a d-liberate inquiry regarding them from patients with salivary tumours.



Fig. 15 —Care 1. A fibrotic area of paroid tissue on the outskirts of the tumour—it was impossible to be sure whether this area was an altered peroid lobule or part of the tumour—it was probably both—ie an area of transition from gland to tumour—(> 72.)

In many cases pieces of salivity gland attached to excised tumours show no bistological abnormalities. In a few cases however chronic inflammation fibrosis and parenchymatious atrophy are present—and while these changes may often be attributable to duct obstruction and other secondary results of the tumours themselves cases such as the following suggest that tumour formation may supervice on previous disease.

Cast I—A man aged 69 years had noticed a lump in front of his car for several months A somewhat irregular mass about 3 centimetries in main diameter and not shaply encapsulated was excised. Microscopically this consisted partity of small masses of rather cellular epublical growth surrounded by much denve fibrous tissue and partity of many lobules of altered parotid tissue which showed an extreme digree of fibroris accompanied by atrophy of acum and ducis and moderate infiltration by round cells. In several places transitions were apparent [Fig. 133] Thick masses of dense hashine fibrous tissue up to 6 millimetries wide and devoid of both parotid and tumour tissue were interspersed through the tumour and some calcification was present in this in places. actuar and duct-like structures already described, but without lumina (Figs 137, 145) Growth and confluence of these produce large masses of many shares

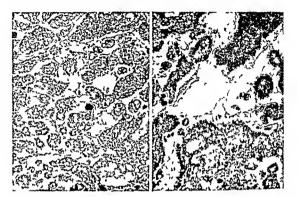


Fig. 137—Solid epithelial clumps and columns with acmar cavities in places and intervening mucoid matrix in a parotid tumour from a woman of 50 years (> 72)

and sizes Epithelial masses may contain solid spherules of cosmophilic secretory material (Fig. 138)

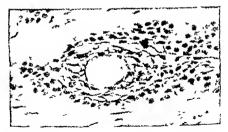


Fig. 138—Solid epithelial mass containing a spherule of cosmophil secretion (× 450)

(e) Epithelial masses with cystic spaces

In large epithelial masses rounded or irregular spaces may appear chiefly by the collection of secretory products of the cells. Sometimes the secretory

(b) Atypical glandular tissue

This is seen in a great variety of forms. These may be acmin or ductular in type, they may be cystic or finely papillary they may contain mucoid or hydrine material or no visible secretion. and they frequently assume convoluted and anastomosing patterns closely resembling those of the intra canalicular structure in mammary fibro adenomas (illustrations by Harvey et al.) Predominance of mucous secreting goblet celled epithelium is sometimes seen as in the cases of Schilling (1921). Lepp (1939), De and Tribedi (1939). However this is not such



Fig. 156—Glandular tissue with epithelial sprouts passing into mucinous matrix simulating cartilage from a submaxillary tumour in a woman of 39 years. (× 72)

a wide departure from normal salivary structure as some writers have made out since mucus secreting cells are present not only in the acim of the mixed glands but also in all salivary ducis

(c) Atypical glandular tissue with marginal epithelial sprouting

A very frequent finding in these tumours particularly well described and depicted by Zymbal, and illustrated in Fig. 136 is the outgrowth of thin strands of epithelium from glandular formations. Sprouts or sprays of cells spread out from these into a surrounding lake of mucinous material where they become very tenuous and the cells often detached. This fraying out of epithelium is a common mode of development of the so called mucoid tissue" and 'cartilage" to be described later.

(d) Solid epithelial formations

These are again of very diverse appearance Many tumours contain solid clumps or columns of epithelium, identical in the characters of their cells with the

acinar and duct-like structures already described, but without lumina (Figs 137, 145) Growth and confluence of these produce large masses of many shapes

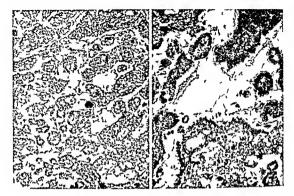


Fig. 137—Solid epithelial clumps and columns with actinar cavities in places, and intercentage mucoid matrix in a parotid turnour from a woman of 50 years. (x 72)

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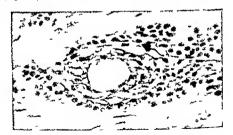


Fig. 138 -- Solid epithelial mass containing a spherule of cosmophil secretion (× 450)

(e) Epithelial masses with cystic spaces

In large epithelial masses rounded or irregular spaces may appear, chiefly by the collection of secretory products of the cells. Sometimes the secretory

spaces assume a characteristic eribriform structure (Fig. 139) which closely resembles that seen in mammary tumours or in adenoid cystic tumours of the skin or nast cavity. These gland like spaces however differ from true arinar and duct lumina in the absence of definite glandular orientation of the epithelial cells around them. Cysts formed by necrosis of tumour tissue are rarely or never seen in the salivary tumours.

(f) Cornifying stratified epithelial structures

Quite commonly parts of these growths develop epidermoid characters stratification prickle cells and cornification (Fig. 140). This squamous celled



Fig. 139 -Cribriform structure in parotid tumour from a man of 25 years (x 72)

metaplasia is comparable with that seen in adenocarcinomas of other glandular organs—and it is not surprising that it should occur commonly in tumours of salivary origin—since developmentally the salivary glands are but outgrowths of the ectodermal buceal epithelium—and indeed the terminal parts of the salivary duest themselves show stratification. Another type of stratified epithelium sometimes seen in these tumours presents an open meshwork resembling that of the stellate reticulum of adam intinomas (Fig. 141) a resemblance again not surprising in view of the close developmental affinities of the original tissues.

(g) Epithelial filaments and networks in a mucinous matrix

Under (c) we have already noticed the frequent fraying out of epithchium to form strands in lakes of mucinous material. This change frequently produces more or less extensive areas of fine epithchal filaments or a meshwork suspended in the mucinous matry. It is this type of structure which has often been called

"myxomatous'—a false name however, since the tissue is not mucoid connective tissue. The epithelial nature of the cells is quite eleur, not only from their frequently obvious derivation by sprouting from glandular tissue but also as Zymbal has most clearly shown, by the presence in the cells of plentiful droplets of mucoid secretion. The mucinous matrix in which the cells are suspended is clearly formed by this secretion of the cells themselves. Sometimes at the margin of a tumour,

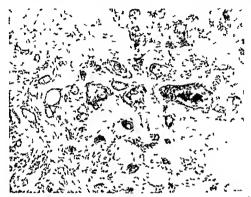


Fig. 140—Cornified cell nests along with some glandular structures in a sublingual tumour from a woman of 39 years (× 75)

direct transformation of normal salivary acini into mucinous epithelial reticulum is apparent (Figs. 142 144)

(h) " Cartilage like ' areas

I put 'cartilage like" in inverted commas deliberately, because I agree with Patey, Zymbal and others that this tissue rarely shows any clost resemblance to cartilage. It represents only a further change in the "myxomatous 'tissue, in which the epithelial cells have become more widely separated and partly detached from one another in the mucinous matrix (Fig. 136).

The peculiar and variable metachromatic staining properties of this matrix do not warrant the conclusions drawn from them by Kux and by Hempleman and Womack These workers upheld the term "mixed" tumours on the ground that different staining techniques enabled them to distinguish epithelial from mesenchymal mucin to identify both types of mucin in the salivary tumours, and to prove the mesenchymal nature of the myxomatous and cartilaginous" areas Thise claims cannot be accepted. It is true that the matrix of these areas stains differently from the mucins within epithelial cells and in the lumina of epithelial cavities. This however, is no proof of its mesenchymal origin gradual.

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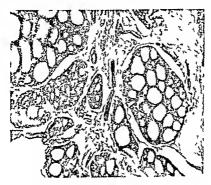


Fig. 139 -Cribriform structure in parotid tumour from a man of 25 years (< 72)

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Under (c) we have already noticed the frequent fraying out of epithelium to form strands in lakes of mucinous material. This change frequently produces more or less extensive areas of fine epithelial filaments or a meshwork, suspended in the mucinous matrix. It is this type of structure which has often been called

for chemical research on the diastase content of salivary tumours and on the chemical changes which may occur in artificial mixtures of salivary diastase and salivary mucus It may well be that the interaction of both secretions of the tumour cells, probably produced in variable proportions in different tumours. accounts for the peculiar and variable physical and staining properties of the mucinous material Clearly, then, we cannot draw any deductions as to the origin of this material from its staining properties

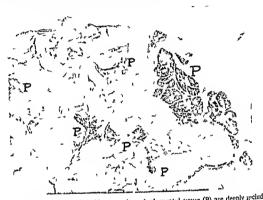


FIG 143 - Case II Islands of darkly stamed residual parotid tissue (P) are deeply included in the mucinous growth (× 5)

It may also be added here that scattering of detached epithelial cells in pools of their own secretion and slow changes in the characters of that secretion are not peculiar to salivary tumours but are seen also in mucoid adenocarcinomas (colloid cancers') of the alimentary canal or breast. In these however, the intra cellular secretion usually appears as a single large droplet of mucus in a signet ring cell, instead of many fine droplets as in the cells of the salivary tumours

(t) Areas with frankly carcinomatous characters

In tumours with a history of recent rapid growth, or of rapid recurrence or metastasis while parts of the tumour may still show structural characters of the foregoing types much of the growth may consist of more cellular anaplastic tissue rich in mitoses The cells may be spheroidal, spindle shaped or pleomorphic, like those of the anaplastic salivary carcinomas described below (see Figs 147, 149) and their arrangement may be in compact epithelial clumps or diffuse

any or all of the Pleomorphism is a striking feature of this group of tumours foregoing varieties of structure may occur in one tumour Obvious gradations chemical changes certainly take place in long stagmant pools of extravasated secretion. As Fry points out, such changes may be related to deficient nutrition,

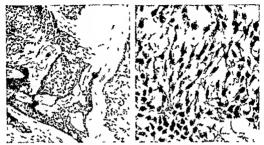


Fig. 141— Adamantinoma like structure with stellate-celled epithelial reticulum in a parotid tumour from a woman of 56 years (x 120 and 400)

since the cells and matrix in the centre of a large mucinous area are remote from blood vessels. Another factor also may operate in producing chemical atteration of the mucinous matrix. This is the probable secretion not only of mucin but



Fig. 142—Margin of a parotid tumour from a woman of 50 years, showing direct transformation of parotid acint (above) into mucinous tumour tissue (below) (> 120)

also of ptyalin by the tumour cells and the chemical effects of this carbohydratesplitting enzyme on the carbohydrate component of the mucin. There is room the one hand to mucinous or "cartilage-like" tumour tissue on the other. The existence of these zones shows clearly, not only that the tumours are derived from salivary epithelium, but also that they take origin, not from a single minute focus at a single moment of time, but progressively from a considerable field of salivary tissue. Dockerty and Mayo reported 4 examples of submaxillary tumours of multicentric origin.

When tumour genesis is progressing simultaneously at many parts of a considerable area of salivary tissue, an intimate admixture of developing tumour

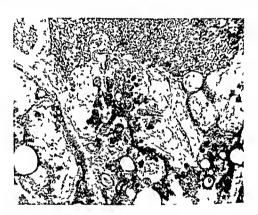


Fig. 145—Case III Neoplastic ducts and clusters of solid neuri interspersed islands of adipose tissue in the stroma (x.72)

and residual salivary tissue may result, with transition zones in many places. A striking instance of this is afforded by the specimen from Case II, depicted in Figs. 143 and 144.

Case II —A man of 26 years had had a slowly enlarging parotid timour for 4 years. Seven months prior to his coming for treatment, this had been incompletely existed and had recurred. Operation disclosed an irregular lobulated rather ill defined mass of growth 3 centimetres in diameter devoid of a capsule and separable only with difficulty from the surrounding tissues. Not only was the tumour imperfectly demarated from the autrounding parotid tissue but as Fig. 143 shows visible residues of parotid tissue by here and there through the tumour and there were also many microscopic residues which the low power photograph does not depict. Many regions of direct transition from these presidues to immort fissue were to be sen (Fig. 144).

The presence of islands of adipose tissue widely scattered through a tumour is to be explained similarly. An example is shown in Fig. 145, from Case III

from one kind of structure to another abound affording clear evidence of the essential identity of the tumour parenchyma in all its variants

Tissue culture from different structural areas of the tumours yields interesting results. Zymbal found that explains from areas of well preserved glandular structure, from solid epithelial masses or from the less degenerated reticular areas were capable of growth in vitro and survival for periods of up to three weeks, but that explaints from advanced reticular or 'cartilage like areas promptly degenerated in vitro. The results accord with the suggestion of Fry, Harvey et al.

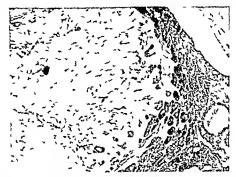


Fig. 144 — Case R A region of direction transformation of parotid acini into mucinous growth (\times 75)

and others that the myxomatous 'and 'cartilaginous' areas are regions of poor nutrition and cell deterioration Zymbal's tissue cultures also showed a variety of forms comparable with those of the timouris—epithelial sheets solid masses networks and isolated cells and further the changes seen in the epithe lium of tumour explants resembled those seen in explants of normal silivary tissue

(8) Relationship of tumour parenchyma to salivary tissue mode of origin of the tumours

It has already been mentioned that direct transitions from salivary again to tumour are sometimes demonstrable. This feature noted by Zymbal, Fry, Harvey et al. is illustrated in Figs. 142. 144. I have seen it unmistakably in eight tumours and I am sure that more careful search by serial or multiple sections of small tumours would reveal it very frequently. The appearances are not to be dismissed as due merely to inflittation of salivary tissue by growth these transition zones show a gradual alteration of the epithelium from normal salivary auint on

or by the subsequent development of a new tumour from predisposed salivary tissue. As Figs 142 144 show, already well-established tumours may show tumour formation from the surrounding salivary tissue still in progress, clearly then removal of the tumour alone at this stage will leave behind potentially neoplastic tissue from which recurrent growth may develop. That multiple neighbouring foci may participate in the formation of a tumour is shown by such specimens as that of Case II, above Just as the bed of mammary tissue around a fibro adenoma often contains small satellite fibro adenomatous foci so the bed of tissue around a salivary tumour may contain multiple potential or actual foci of growth

An interesting observation of McFarland's (1936) is relevant here. This is that recurrence is more likely to follow removal of small tumours than of large ones, and McFarland advises that tumours should not be removed until they have attained "the size of a lemon". This seeming anomaly is readily understood in the light of what has just been said. The smaller a tumour, the more likely it is that tumour genesis from salivary tissue is incomplete and still in progress or that satellite tumour foer not yet confluent with the main mass are present, and therefore the greater the likelihood that simple enucleation will leave behind the germs of further growth. On the other hand, when a tumour is permitted to grow to a large size before its removal, it is then likely to have incorporated the whole of the potentially neoplastic field of tissue and to have become more completely encapsulated, hence its enucleation is correspondingly less likely to leave behind the seeds of recurrent growth.

In most cases the microscopical structure of a salivary tumour is an unreliable guide to prognosis On the one hand, recurrence may follow removal of tumours of the most benign looking histological type, and on the other hand cellular active looking growths from which recurrence was anticipated may fail to recur paradoxes" of prognosis have been fully discussed in the several papers by McFarland as well as by Patey McFarland (1942) found, however, that tumours in which epithelium predominates have a less favourable outlook than those in which mucinous and stromal tissue predominates, the former recutting in 60 per cent of eases and the latter in 38 per cent a difference which accords well with Zymbal's conclusion from tissue cultures that the cells of mucinous areas are of poor proliferative power and viability McFarland also found that tumours with a predominant 'carcinomatoid' structure give a high proportion of recurrences, while the recurrence rate of growths with prominent papillary structure is the highest of all, over 80 per cent In assessing prognosis, the clinical rate of growth of a tumour should be considered in conjunction with its histological tumours which have increased rapidly and which show carcinomatous appearances microscopically have a bad prognosis

(12) Metastasis

Lymphatic or blood borne metastases from salivary tumours of the pleo morphic class are rare. Instances have been recorded by Wood Ahlbom Fitzwilliams Ewing, Dockerty and Mayo. Bland Sutton (1906 Fig. 56) depicted a paroid tumour which had been growing slowly for 17 years and which then grew rapidly and infested the lymph glands, and destroyed the patient in six

Case III —A well encounterhed rounded puroted tumour was removed from a woman of 23 years. The whole tumour which appeared well encapsulated had a similar structure consisting largely of epithelial clusters resembling solid cann distributed around branching tubules and solid epithelial strands in a way generally re-embling the relationship of lobules and ducts in normal salwary tissue interspersed throughout were islands of normal looking adipose tissue.

In this case I conceive that neoplastic change has overtaken the whole of the salivary epithelium in the susceptible area including both duets and acini. The acini like clusters are salivary acini which are now neoplastic the duct like tubules are neoplastic former salivary duets and the islands of adipose tissue are those of the original parotid gland persisting in the tumour with the same relationships to the now neoplastic tissues as to the former normal tissues. Others who have seen islands of adipose tissue in salivary tumours include Wood (Case 2) and Har.ev et al. (Fig. 45)

The question whether the tumours take origin mainly from salivary acini or ducts is of little moment. It is clear that both participate. We have noted the direct transformation of acini into tumour, and the frequent presence in the tumours of duct like structures with characteristic two layered epithelium, and specimens like that of Case III point clearly to simultaneous participation of the whole of the epithelial elements in an area of salivary tissue ducts and lobules of acini alike. The mode of origin of the tumours parallels that of maintary epithelium including both ducts and acini.

(9) Stroma and capsule

Even some of those who are satisfied that the tumours are of purely epithelia nature have confused stroma and mucinous and pseudo cartilaginous areas Again it must be insisted that the latter belong not to the stroma but to the epithelial parenchyma of the tumours. The stromal connective tissues and the mucinous material may mingle intimately producing appearances easily mistal en for mucioud change in connective tissue. Lakes of mucinous secretion often have indefinite borders and seepage of the material into the neighbouring stroma produces mixtures of mucin and collagen with correspondingly variegated stating properties. By using appropriate stams however (e.g. Ehrlich's haematoxylin followed by light counterstaining by pierie acid or van Gieson's counterstainly, the two ingredients of these mixtures can often be rendered beautifully distinct. As Hurvey et al. have shown elastic as well as collagen fibres may mingle with mucinous matrix. Pools of mucinous secretion may also flow around and isolate blood vessels and haemorthages into the secretion may occur.

It may be pointed out here that many of the appearances produced by mingling of stromal and patenchymatous elements seen in these tumours are paralleled in mucoid or colloid carcinomas of other organs and in mucoid extravasations such as pseudo myxoma pentones. In these also we see intimate admixtures of mucinous secretion and connective tissues sometimes accompanied by hydine changes in the latter.

Changes in the stroma proper of salivary tumours include fibrosis alteration of elastic tissue hyaline chinges, collections of leucocytes calcification and rarely, osseous or cartilaginous mutaplasa. Increase of collagenous tissue with

metastasizing carcinomas. In the case of salivary neoplasms most of the immours occupy an intermediate or borderline position in the scale of behaviour. The prognostic question here should not be, "Is this tumour innocent or malignant?", but 'How innocent, or malignant, is this particular iumour likely to be?' How far we can answer this question has been indicated above.

Do relatively benign tumours become malignant, and do recurrences show enhanced malignancy? McFarland (1936) and Patey answered this question

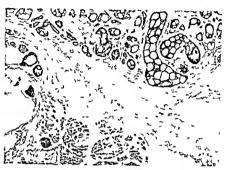


Fig. 148—Case V Recurrent growth of embriform structure infiltrating cervical fascia and platysma muscle (× 40)

in the negative, and concluded that, while different tumours show different degrees of malignancy a single tumour shows little or no change of structure or rate of growth in its recurrences. While this is probably true of the majority of tumours there are I believe exceptions. Thus in Wood's Case 4 a parotid tumour of slow growth had been present for 53 years and had then grown rapidly in the list few months and microscopic examination showed squamous celled carcinoma in an otherwise typical mixed tumour. Bland Sutton's case with metastases referred to above, gave a similar history, and in my Case IV above the recurrent growth and the subsequent metastases showed carcinomatous structure which was not observed in the growth on its first removal. The following Case V is also of interest in this respect.

Case V—In November 1938 a woman aged 37 attended hospital with a small tumour noticed for 5 months close to the left angle of the mandible. This was thought to be a sebaceous cyst and was excised. It was a well-defined spherical mass I centimetre in diameter microscopically a typical pleomorphic salivary tumour of well differentiated type in which tubular and ci-hirofinm structures (like those of Fig. 139) predominated it had a well defined fibrous capsule except at one point where the tumour ususe lay immediately contiguous with parolid tussue. The tumour soon recurred and was again operated on in October 1939, when an irregular mass about 3 centimetres in main event and not separable from the parolid tissue was excised. Microscopically this showed a

months The following is an example of metastasis both to lymph glands and by the blood stream

Case IV—In June 1923 a boy of 16 years first not ced a small swelling in the left parotide gland. This gradually enlarged until in June 1925 when it was exceed it was as large as a hen a seg and somewhat cystic. Microscope, examination showed the typical structure of a glandular and mucnous moved turnour. Early in 1930 the patient complained of pain in the ear and at operation a mass of recurrent growth deep in the parotid gland was incompletely removed the microscopial report was mixed salivary gland turnour with corunnatious areas locally malignant. Radium was applied apparently with



Fig. 147 - Case IV Mutastatic spheroidal celled growth in a cervical lymph gland (x 150)

good result. Late in 1934 enlarged glands first appeared in the neck these increased and were excised on Murch 1935 and radium was smerted. The largest of the excised glands was 4 centimetres in diameter and microscopie examination showed carcinomatous tissue resembling the carcinomatous areas of the recurrent salvary tunnour removed in 1930 (Fig. 147). Skiagrams now showed scattered small metastases in both lungs and also a probable metastasis in a rib. A year later in April 1936 skiagrams showed many large deposits in the lungs and a spherical timour is meters in diameter had developed from the rib. The patient died in June at the age of 29 and 13 years from the first appearance of the tumour.

(13) Innocent or malignant?

Because of their slow growth their supposed encapsulation and the rarity of metastasis the phomorphic salivary tumours have often been classed as 'benign This fallacious idea cannot be too strongly discouraged Tumours which are often demonstrably not encapsulated which frequently recur after removal which may widely inflitrate surrounding tissues and which occasionally metastasize trie far from benign. The truth is that here as with many other kinds of neoplasms innocent and 'malignant are only relative terms and all gradations of

behaviour as well as of structure are to be seen between highly differentiated slowly growing innocuous adenomas and poorly differentiated infiltrating and

adenocarcinomas which merge insensibly into the group of anaplastic carcinomas now to be described

ANAPLASTIC CARCINOMAS OF THE SALIVARY GLANDS

I have studied four salivary carcinomas which appeared to be frankly malignant from their onset, growing rapidly, producing metastases, killing within relatively short periods, and consisting of highly cellular rapidly proliferating issue not at once recognizably related to that of the previous group. From careful study of these four cases, however, as well as from my review of previous reports of salivary carcinomas, I am sure that these growths differ from those of the pleomorphic group only in their rate of growth and degree of malignancy and not in their



Fig 150—Case VII Polyhedral and spindle-celled epithelial clumps in a metastasis in the adrenal gland (× 150)

histogenesis. My four examples of anaplastic carcinoma, all of the parotid gland, may be briefly described

Case VI—A man aged 61 had had a rapidly increasing mass in the left parotid region for 10 months before he died. Necropsis revealed a large hard white parotid tumour with metastases in the cervical lymph glands many nodules in the skin of the neck and thorax fewer skin nodules in the lower parts of the trunk and thighs and multiple metastases in the lungs parietal pleura heart (a single nodule in the wall of the left auricle) liver spleen into during mater abdominal and riguinal lymph glands and pertineum Histologi—A cellular spheroidal-celled carcinoma with many mitoses in places a moderate amount of connective tissue stroms between epithical strands showing some hyaline change recalling the appearance of cellular parts of tumours of the pleomorphic group

Care III.—For 16 months before he died a man aged 71 had had a rapidly increasing left parotid lumour which attained an enormous size. Necropry showed a huge solid white tumour with satellite skin nodules around it metastases in the cervical and upper

structure similar to the previous specimen but was infiltrating the surrounding partoll and cervical tissue (Fig. 148). X ray therapy was carried out. The lumour recruite again early in 1941 and in May an ill defined mass of growth about 4 centimetres in diameter was excised. Microscopically this showed in addition to some cribriform structure many areas of undifferentiated spheroidal celled carcinomatous growth (Fig. 149). In May 1942, the patient developed pleural effusion and cough and a skiagram strongly suggested the presence of small scattered metastases in the lungs.

The foregoing observations show that on occasions salivary tumouts do display accelerated rates of growth with enhanced malignancy sometimes demonstrably

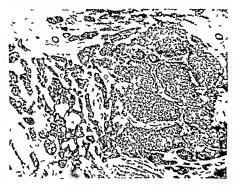


Fig. 149—Case V —Further recurrence of growth of undifferentiated carcinomatous structure (~ 75)

accompanied by structural de differentiation. I agree however that this change is improperly described by saying that benign tumours become matignant the tumours are malignant all along but their rate of proliferation and degree of malignancy may sometimes show more or less abrupt increases. Whether such increases are ever due to surgical trauma is doubtful. Wood is and Bland Sutton is cases showed accelerated growth prior to operation.

Because these tumours are always either potentially or actually malignant I cannot concur with Harvey et al. and other workers in calling them all adenomas. This title though commendable in so far as it emphasizes the simple glandular origin and nature of the growths gives a false estimate, of their benignancy. If we are to have a reasonably correct designation for the whole group formerly called mixed tumours it cannot be made any simpler than pleomorphic adenomas and adenocarcinomas. This recognizes the mixed or variable structure of the tumours and the variable behaviour which they display ranging from the rare benign adenomas to frankly malignant

These four tumours, though highly malignant, nevertheless show traces of the structural characters familiar in the pleomorphic tumours, namely hyaline changes in the stroma, secretion by the tumour cells (signet-ring cells in Case VII) and spindle celled epithelial masses. I believe that no sharp line of demarcation can be drawn between the most malignant tumours of pleomorphic type and the still more malignant growths like those just described, these merely represent the extreme end of the scale of malignancy. I believe that, excluding the adeno lymphomas, all salivary tumours have in the words of Fry, 'the same essential structure, the difference between them being a difference in degree of malignancy and in the amount of secondary changes.'

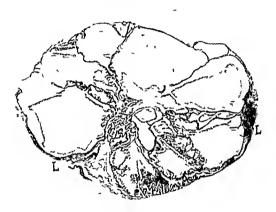


Fig. 152—Case X. Whole section of adeno-lymphoma, showing its polycystic and papillary structure and peripheral areas of lymphoid tissue (L). (X >)

Salivary sarcomas

This is the proper place to refer briefly to the supposed occurrence of sarcomas in the salivary glands. I have yet to see a report of a case in which I could accept this diagnosis as even probable. As was noted early in this chapter, the pleo morphic tumours, especially those with diffuse mucinous areas, were formerly often classed as 'sarcomas' or myxosarcomas'. Excluding these and excluding also cases of secondary leukaemic and lymphosarcomatous infiltration of salivary tissue (one cause of Mikuliez's syndrome), there remain only very rare instances of supposed sarcoma' of the salivary glands, and examination of these makes it clear that in most or all of them the tumours were not sarcoma's but anaplastic carcinomas like those described above. As long ago as 1910,

mediastinal lymph glands and in the lungs fiver spleen and both adrenal glands. The primary tumour had directly invaded the thyroid gland and the internal jugular vein Histology—A highly cellular carcinoma of rather variable structure. Parts consist of large polyhedral and irregular cells arranged diffusely and with lattle tendency to epithelial grouping some of the cells are of signer ring form containing dropts of secretion Other parts consist of clongated and spindle shaped cells often arranged in epithelial clumps (Fire 150). Mitosex are very numerous sometimes multipolar and some of the timour cells are large irregular and multinucleated. Stroma is scanly

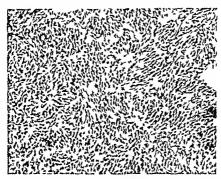


Fig. 151 - Case III Spindle-celled sarcoma like structure of a metastasis in the lung (x 150)

Case VIII—A woman 37 years old at her death had first noticed a lump in the laft partial deat 31 years previously. Operation 2 month after this disclosed a frashle tascular tumour the size of a golf ball in the substance of the partial gland microscopically a cellular anaplastic carcinomy. Repeated radium treatments were carried out each time with temporary benefit followed by recurrence of the growth. Veryons showed a huge soft partial discusses and a single metastasse of centimetres in dame ere in the right breast. No metastases were found in lymph glands. Histobey—Parts of the tumours show clumped spindle celled groups similar to those of Fig. 150. but the bulk of the tissue consists of diffusely arranged spindle-cells resembling a spindle rell sarcoma (Fig. 151). Mitovis are plentiful and stroma scartly.

Case IX—A man of 78 s.ars had noteced a mass growing in the parout region for 7 months on examination this was a large mass invading the skin and adherent to deep structures. Excision was attempted but was incomplete and the patient died of recurrence a few months later (in energoes). The existed mass was 65 centimettes in diameter parily well defined partly infiltrating surrounding tissus including the istemomisted muscle. The tissue was firm and white with degenerated and haemorthage, areas but no mucrous areas or other extence of an antecedent muted tumour. Histology—Acciliate spheroidal-celled and spindle-celled carcinoma most of which shows definite epithelial clumping with intervening strands of partly hyadine connective itsue but with other parts more diffuse in structure. Mitoses are many and there are some large irregular multimosterated tumour cells.

Microscopically it had the characteristic structure of a cystic papillary adeno-lymphona (Fig. 153). Most of the lymphoid ussue lay around the periphery beneath the capsule strongly suggesting that the growth occupied a lymph gland. There was no recurrence 4 years after removal.

Case XI—A man of 51 years had noticed an enlarging lump below the left ear for 2 years. Examination showed a rounded mobile swelling 4 centimetres in diameter, and operation disclosed a thick walled cystic mass with turbid yellow contents thought to be an enlarged, probably tuberculous lymph gland. Microscopic examination of a piece of excised tissue however showed the typical structure of cystic papillary adenolymphoma with abundant lymphoid tissue in the stroma.

(1) Clinical characters

(a) Age incidence

On the average, adeno lymphomas appear later in life than the pleomorphic salivary tumours The ages in decades of the cases collected by Plaut were

| Decades - | ~ , | 1 | 2 | 3 | 4 | 5 | 6 | 7 | over 70 |
|-------------|-----|---|---|---|---|----|----|----|---------|
| No of cases | - | 2 | 2 | 1 | 5 | 13 | 20 | 13 | 5 |

Youngest, 2½ years, oldest 92, average 52 years

(b) Sex

In sharp contrast with the pleomorphic tumours, adeno lymphomas show a great preponderance of males—in Plaut's collected cases, 50 males to 12 females It would be of interest to determine whether or not heterotopic salivary tissue in lymph glands occurs more often in men than women.

(c) Situation

With few exceptions the tumours are related to the parotid gland being situated usually quite superficially and often separate from the gland, or occasion ally in its substance. A few of the tumours have been related to the submaxiliary gland. Two cases with bilaterial tumours have been reported (Plaut)

(d) Duration and rate of growth

Most of the tumours are of slow growth. The pre operative duration varies from a few weeks to many years, with an average of about 6 years. Even after long duration some tumours are still quite small, e.g. in the fourth case of Carmichael et al. the tumour was only 2 centimetres in diameter after 30 years. On the other hand, some of the tumours have attained a large size in much shorter periods.

(e) Prognosis

With rare exceptions the tumours are encapsulated, easy to shell out completely, and quite benign Recurrence is unusual, and finally malignant characters, as in the cases of Stohr and Risak, and Sobolew (references by Plaut), are rare

Chevassu deprecated the tendency to give the name sarcoma to every mahignant tumour the elements of which are arranged diffusely. This warning still often neglected along with the histology of the four examples of anaplastic carcinoma described above is all that need be said of sarcoma of the salivary glands

SALIVARY ADENO LYMPHOMAS

These relatively rare growths, which constitute less than 10 per cent of all salivary timours are highly distinctive and unrelated to the common pleomorphic adenomas and adenocarcinomas. Under the quite appropriate alternative name of papillary cystadenoma they were first described in 1910 by Albrecht and Azzi, who noticed the close resemblance of their epithelium to that of salivary ducts In 1923 Nicholson reported the first English cases describing the timours as

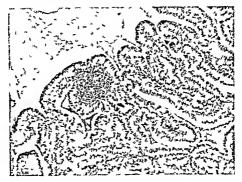


Fig 153 - Case X Adeno lymphoma (x 80)

adenomas of heterotopic salivary tissue in the preparotid lymph glands. The best general account of these timours is that of Carmiehael. Davie and Stoward (1935) who reviewed 26 previously reported cases and added 8 of their own By 1942. Plaut was able to bring the total number of reported cases up to 64. I have studied two specimens of typical adeno lymphoma, the details of which are briefly as follow.

Case X—A, man of 67 years had had a slowly enlarging mass below the left car for 24 years. Exceed intact this was an encapsulated ovoid mass resembling an enlarged lymph gland $2.5 \times 2.2 \times 2$ centimetres. On section it consisted of several large cystic spaces occupied by gelsinous material and into which projected some finges of papillary rowth some crescentic artisas of solid tissue lay at the periphery in places (Fig. 182).

'onkocytoma" should be discarded Kraissl and Stout's suggestion that adeno lymphomas arise from vestiges of orbital salivary glands is wholly speculative

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(2) Structure

(a) Naked eye characters

The tumours are rounded, ovoid or slightly flattened, with an even or slightly lobulated smooth surface and a distinct capsule. On section, they may be wholly boild but are much more often partly cystic. The tumour tissue forms shaggy papillary fringes or masses projecting into the cystic spaces. The cyst contents may be mucoid, mifky, or turbid resembling liquid caseous material or pus in which event the surgeon may easily mistake the tumour for a tuberculous lymph gland as in my Case XI.

(b) Histology

The microscopic structure of the growth is highly distinctive—showing a more or less intimate mixture of lymphoid stroma with a characteristic epithelial parenchyma which forms tubules or lines the cystic spaces and the branching intra-cystic papillary projections. The epithelium closely resembles that of the medium sized duets of the salivary glands. It consists of a double layer of cells comprising a regular palisade of tall columnar cosmophilic cells which reach the free surface and have their nuclei in an even row towards the free margin and a basal layer of smaller irregular cells usually fewer in number and less regularly spaced than the tall cells. The stroma between the epithelial tubules or cysts or forming the cores of the branching papillary structure is infiltrated by few or many lymphocytes or beset with prominent lymphod follicles. Some plasma cells or cosmophil leucocytes may mingle with the lymphoeytes. Once fibrous stroma may be present in places, and the capsule of the tumour is fibrous and well defined.

(3) Histogenesis

Nicholson's view that these tumours arise from heterotopic salivary tissue in lymph glands has already been mentioned. Before reporting his two cases Nicholson had already (1922) noted the observation of Neisse that heterotopic salivary tubules are frequently present in the preparotid lymph glands of infants and had himself reported an example of persistence of such tubules in an adult Moreover he had no doubt that the two tumours which he described were indeed within lymph glands an opinion which the structure in my Case X also strongly supports. The frequent separateness of the tumours from the paroid gland and the frequency with which at operation they are regarded as enlarged lymph glands also support Nicholsons s view which indeed has gained wide acceptance and which I am satisfied is the correct one. Adeno lymphoma , whilst not an ideal name is a brief and descriptively convenient one expressing the combination of optificial glandular and lymphoid tissue in these tumours though papillary cystadenoma and salivary adenoma of lymph glands are also quite appropriate.

The opinion of some workers that the tumours arise from branchial remains is groundless as well as superfluous So also is the view that they arise from a special kind of epithelial cell seen in the salivary gland of old people the pyknocyte' of Zimmermann or onkocyte of Hamperi and Jaffe's ugly name

irregular glandular spaces. In places the epithelium has a prominent cuticular margin. The cytoplasm is distinctly cosmophilic and foamy in structure because it contains

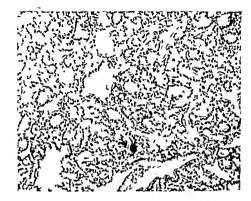


Fig 154 - Case VI Nasal adenocarcinoma (× 120)

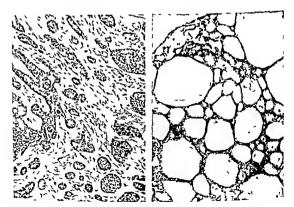


Fig 155 - Case VII Nasal adenocarcinoma (x 120)

CHAPTER 18

EPITHELIAL TUMOURS OF THE NASAL AND PARANASAL CAVITIES

ALTHOUGH most parts of the nasal and paranasal cavities are lined not by squamous stratified epithelium but by pseudo stratified respiratory epithelium it is not surprising that many of the epithelial timours of these cavities are of squamous structure. The nasal epithelium is derived mainly from the ectoderm, it persists in the squamous form in the region of the nostrils and as in the bronch: the respiratory epithelium readily undergoes squamous conversion in neoplasms. Some tumours, however retain the structure of the pseudo stratified epithelium, with or without cilia. Other tumours the nasal adenocarcinomas clearly arise from the nasal glands. A special group of tumours involving the maxillary antrum and possessing a variable structure often described as resembling the cystic basal cell carcinomas of the skin or the so-called mixed tumours of the salvary glands still cause confliction. It shall advance reasons for believing many of these to be adamantinomas' arising from the paradental epithelial residues. It will be useful to outline first my own observations of nasal tumours.

ELEVEN PERSONALLY STUDIED NASAL EPITHELIAL TUMOURS

(1) Epidermoid carcinoma

Case 1—Male aged 56 Pieces of tumour curetted from the sphenoid and ethinoid sinuses showed active squamous-cell careinoma

Case II —Fernale aged 64 Masses of tumour removed from the maxillary antrum showed well differentiated squamous-cell carcinoma

Care III — Male aged 69 Masses of tumour removed from the maxillary antrum showed non-cornifying squamous-cell careinoma

Care IV —Female aged 67 Preces of tumour removed from the maxillary antrum showed diffuse cellular careinoma of epidermoid type

Case V—Male aged 54. History—Pain and swelling of face for 15 months. Accopts showed right antrum and surrounding bone replaced by a huge firm growth with great enlargement of the face and invasion of the skin of the cheek and eyelid. Tumour deposits were present in the upper posterior cervical lymph glands but there were no remote metatiases. Histology—Both primary growth and lymph nodal metastases showed diffusely cellular anaplastic epidermoid caretinoma in parts so undifferentiated as not to be recognizably enthelial in character.

(2) Adenocarcinoma

Case 11—A man aged 68 had noticed increasing masal obstruction and discharge for 4 years and more recent swelling of the nose and left side of the face. Examination showed the left nasal cavity to be distended by a mass of frable growth and skiagrams showed enlargement and opacity of the maxillary sinus. Deep X ray therapy produced no noticeable impronement in the tumour and 5 years later the patient was reported by relatives to have extensive ulcerating growth. **Histology* (Fig. 154)—Pieces of the nasal portion of the tumour show well-differentiated adenocarcinoma consisting of low columns or pyramidal cells arranged in a single layer around well-diffined acris or

Case VII—A man aged 70 had had symptoms of an enlarging nasal and antial timour for 3 years Examination and exploratory operation showed large masses of growth in the right half of the nasal cavity and in the antirum—the anterior bony wall of the antirum was destroyed and a mass of growth projected externally—Histology (Fig. 155)—Pees of tirsue removed from the nasal, antiral and externally projecting parts of the growth all show similar characters—The tumour is an adenocarcinoma with areas of acmar structure.

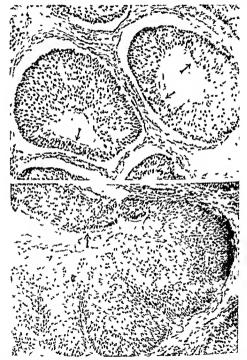


Fig. 158—Case X. Details of nasal "papilloma the epithelium of which is partly of chiated respiratory type (marked by arrows) and partly of squamous stratified type (K 120)

multiple fine droplets of secretion which are often distributed radially in the cells. The nuclei are basal spherical fairly uniform in size about \$\mu\$ in diameter each with a single nucleous and an evenly stained fine chromatin meshwork. In motive figures are rare. The action cavities contain some cosmophile secretion.



Fig 156 - Case IX Nasal mucoid adenocarcinoma (x 120)



Fig 157 - Case X Nasal papilloma (y 6)

had caused a perforation into the antrum and blood had come from the nose.) Operation disclosed a finable mass of growth distending the antrum, this was easily removed except along the nasal wall to which it adhered firmly Radium was inserted. Microscopical examination (Fig. 159) showed the tumour to consist of well defined small and large masses and trabeculae of epithelial tissue in places closely like those of the cystic basil-cell carcinomas of the skin in other places resembling adamantinoma of the piws. The marginal parts of the masses were formed of closely set palisades of cubical or columnar cells. The cells of the central parts of the masses were less compact with many rounded intercellular spaces which either appeared empty or contained some pale cosmophic

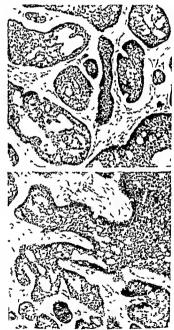


Fig 159B - Case XI Basal cell carcinoma (adamantinoma) of antrum (× 120)

secretion These spaces gave many of the epithelial masses a cribiform pseudoglandular appearance but as in the pleomorphic tumours of the salivary glands and in adamantinomas , the cells hung the spaces were flattened and showed no glandular similar to that of Case VI but with many areas of imperfectly differentiated structure consisting of irregular gland spaces lined by double or triple layers of epithelial cells solid epithelial cords or masses or masses shelded by dilated actinar spaces giving a embriform or honeycombed appearance. Mitotic figures are present in modurate numbers

Case VIII - Male aged 68 Pieces of tumour removed from the ethmoid region showed adenocarcinoma resembling that of the previous case

Case IX—A small sessile greysh tumour I centum tre in diameter was removed from the lateral wait of the nasal cavity of a man of 75 years Histology (Fig. 156)—It is a well differentiated papillary mucoud adenocarcinoma consisting of convoluted and branching layers of columnar-cell epithelium including many mucus-containing goblet cells along with quantities of ettra-cellular mucnous secretion. Most of the epithelium is single layered but in places it appears pseudo stratified. No ciliated cells can be found Moderate numbers of mitotic fleures are present.

(3) Papillary respiratory epithelial carcinoma ' papilloma'

Case X—A mucous polyp of unrecorded duration was removed from the nast cavity of a man of 59 years. Microscoperolly (Figs 157 and 158), it proved unexpectedly to be a papillary carcinoma clearly derived from the calcated pseudo-stratified respiratory epithelium. The surface of the growth and folded branching spaces within it were clothed by a third layer of epithelium partly of typical clinated pseudo-stratified type and partly of stratified squamoid type the two alternating and merging with one another. Where the squamous changes were prominent there were many solid climps and columns of epithelium occupied centrally by large masses of swellen polygonal and squamous cells but without cormification. Mixtue figures were plentiful. Two months later a recurrent growth was removed from the maxillary antium—and this thowed similar characters with however more advanced squamous change and a coarset papillary structure



Fig 159A- Case XI Basal-cell carcinoma (adamantinoma) of antrum (x 120)

(4) Carcinoma of so-called basal-cell type adamantinoma

Case YI—A woman aged 46 complained of enlargement of the left side of the face of 4 years duration recently a swelling of the alveolar tidge had necessitated cutting away part of her denial plate and the left side of her nose was growing larger (When she had had all her teeth removed 21 years previously extraction of the left upper incisor

anaplastic ones, and the latter may be so cellular and diffuse in structure that parts of them may be microscopically indistinguishable from sarcoma, as in my Case V Epidermoid carcinomas are seldom of long duration, and the more anaplastic often kill within a few months of the onset of symptoms Metastass to the upper deep cervical lymph glands is not unusual in the later stages, but remote metastasis is not commonly recorded MacComb and Martin reported metastases in 19 of 65 cases of malignant masal tumours (29 per cent), most of these were in the cervical lymph glands, remote metastasis occurred in only 6 cases, to lungs, boncs, liver and brain, in all but one case with metastases the tumours were epidermoid carcinomas Ringertz saw metastases in 32 of 119 squamous cell carcinomas (27 per cent) Gachtgens (1933) saw a case with multiple blood borne metastases in the viscera and bones from a small unsuspected primary nasal tumour

(2) Adenocarcinomas

The structure of some of these, as in my Cases VI, VII and VIII, makes it clear that they have arisen from the glands of the nasal mucosa. Highly mucoid tumours, such as that of Case IX, may arise rather from the goblet celled surface epithelium. Parts of some of the adenocarcinomas show a variety of acmar, mucoid, cribriform and solid structures, resembling that seen in the pleomorphic salivary tumours. The rate of growth is decidedly less than that of the epidermoid tumours, durations of several or many years being common, as in Cases VI and VII. The slower growing, best differentiated glandular growths of the nasal mucosa, Ringertz and others have called "adenomas", admitting, however, that recurrence is frequent and that the distinction from carcinoma is indefinite. The adenocarcinomas eventually destroy the surrounding bones, infiltrate soft tissues, and ulcerate in the mouth, pharynx or externally. I do not know of any adequately substantiated examples of metastasis, MacComb and Martin mention one case, but without details. None of Ringertz's 10 cases showed metastasis.

(3) Basal-cell carcinomas and adamantinomas

Adamantinomas are, of course, not primarily nasal tumours, but from the close anatomical relationship of the roots of the maxillary teeth to the floor of the antrum of Highmore, it is obvious that tumours derived from the maxillary paradental residues must in many cises grow into the antral cavity (For examples see the cases of Vorzimer and Perla (1932), and Simmons (1928) Nos 3 and 9) Yet this is often overlooked by pathologists who accordingly continue to confuse such tumours with 'cystic adenoid carcinoma", "salivary tumour', or cell carcinoma", as in my Case XI above Geschickter's list of nasal and paranasal tumours did not mention adamantinoma and I suspect that some at least of his 15 'cystic basal cell carcinomas" (including that of his Fig 13), and also the supposed 'adenocaremoma of Schneiderian type" depicted in his Fig 18 may really have been adamantmomas. The diversity of structure and cystic change seen in adamantinomas and the close resemblance of some of these to structures seen in basal cell caremomas of the skin and in the pleomorphic salivary tumours account for the variety of designations of the antral adamanti nomas when their true nature is not recognized Careful search of several different orientation. Some of the epithelal masses contained a loose meshwork of cells resembling the stellate reticulum of adamantinomas. No prackle cells or comification could be found. Mitothe figures were scanly. Comment—This turnour was at first identified by me as a cysise adenoid basal-cell carendoma. Of the astrum and I realized its true identity only later. It it had predominantly morbide the alwester region of the jaw it would undoubtedly have been correctly identified at first. The history of injury to the antrum during extraction of the teeth serves to remund us how close the roots of the teeth for to this cavity, and therefore how readily a turnour derived from the paradental residues might extend primarily into the antrum.

STRUCTURAL TYPES OF NASAL TUMOURS AND THEIR BEHAVIOUR

These have been exemplified in the foregoing cases. The monograph of Ringertz (1938) contains much valuable information and excellent photomicro graphs. Geschickter (1935) also has described and depicted examples.

(1) Epidermnid and respiratory papillomas and carcinomas

(a) Pavillomas

Papillomas clothed by squamous stratified or respiratory epithelium are rare and, as with most other papillary growths of mucous membranes their benignancy open to doubt. An excellent paper by kramer and Som (1935) reviewed 85 tumours of this kind. These affected males more often than females occurred mainly in middle age and arose more often in the paranasal sinuses-usually the ethmoid or marillary-than in the nasal cavity. There was often a long history of nasal infection but the causative influence of this was doubtful. All kinds of epithelium, respiratory squamous and transitional might be seen in one tumour Recurrence after removal was usual because there is usually diffuse involvement of the nasal mucosa-true papillomatosis The interval prior to recurrence varied greatly and might be as long as 8 years Repeated recurrences might take place during many years without the supervention of invasive characters or histological malignancy Carcinomatous change was however a common termination. Ringertz's account of 10 new cases confirmed the greater incidence in males, the occurrence of multicentric papillomatosis, the variety of the epithelium, the proneness to recur and to become malignant It seems cle ir that no sharp distinction can be made between benign papillomas and papillary carcinomas. Tumours IX and X above would certainly have been included as ' papillomas by Kramer and Som Case X shows how readily parts of a tumour of respiratory epithelial type may assume a well differ entiated squamous papillary architecture

(b) Epidermoid Carcinomas

These, usually of the ordinary squamous celled type and less often of the hympho epithelioma type are the commonest nasal tumours. The maxiliary antrum is their most frequent site of origin but lympho epitheliomas are more often nasal than antral (Geschickter). The cancerous epithelium may exhibit to varying degrees the characters of respiratory peudo stratified epithelium-(excellent photos by Ringertz) but aquimous change, is nearly always prominent in malignant tumours. Like the carcinomas of the fauees and pharying the nasal carcinomas differ greatly from one another in their degrees of differentiated. Tumours of highly keratinizing type are less frequent than poorly differentiated.

of arsenic smelters, the flock had had attacks of arsenical poisoning, and arenic was present in small quantities in the tumours and organs of the cancerous animals. Nieberle also referred to endemic nasal tumours in horses and cattle, reported from Sweden by Sternstrom and Magnusson. The nasal and paranasal cavities are among the commonest sites of carcinoma in horses (Feldman, 1932). Experimental investigation of the possible carcinogenic action of inhaled nickel, chromium, arsenic and their compounds, and of other occupational fumes and dusts is needed.

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sections of a tumour may be necessary in order to discover typical adamantino matous epithelium with well formed stellate reticulum, this applied to my Case XI

The ease with which adamantmomas may be confused with 'basaliomas' and "salivary tumours was recognized by Ringertz, who spoke of a 'basa lioma type' of adamantinoma and who said "if the whole adamantinoma is of the basalioma type, it is impossible to distinguish the growth histologically from a salivary gland tumor And again, he rightly insisted 'in the case of maxillary tumors it is often impossible to determine whether the tumor arose in the alveolar process or in the sinuses'

I do not deny that true nasal tumours of basal cell type occur. Indeed in view of the closely similar structures to be seen in basal cell carcinomas of the skin the pleomorphic salivary tumours and the adamantinomas it might be expected that some of the tumours of the nasal epithelia would display similar structures. But it is certain that these tumours and the anitral and nasal adamanti nomas have often been confused with one another, especially when only one or two micro sections of the tumours have been examined and which of any given worker's diagnoses are correct and which incorrect it is often impossible to say I believe that the more thoroughly tumours of basal cell appearance are examined the higher the proportion of them that will be recognized as being adamantinomas

The behaviour of the antral adamantinomas resembles that of their mandibular and alscolar counterparts. They are of slow growth distending and destroying the surrounding bone difficult to eradicate and usually fatal, but rarely producing metastages.

THE CAUSATION OF NASAL TUMOURS

The age distribution of nasal and paranasal carcinomas is about that of carcinomas in general they are unusual in young people and most prevalent in the sixth and seventh decades. The mean age of my 10 cases was 64 years and the mean age of MacComb and Martin s 65 patients with malignant nasal tumours. \$8 of which were carcinomas was 55 years. In most series of cases, there have been more males than females—8 to 2 in my series. 41 to 24 in MacComb and Martin s. but in Ringertz s series there were more women than men.

The evidence that either the ordinary infections of the nasal cavity and sinuses or the presence of simple inflammatory polypi predisposes to careinoma is inconoliusive but Ringertz beheves that there is adequate evidence of such a predisposition. In Gachigen is crise the patient had had rhinoseleroma six years earlier and the rest of the nasal mucosa showed polypoid changes and squamous metaplasia and two of MacComb and Martin is cases of epidermoid circinoma had rhinoseleroma.

There is evidence that occupational exposure to certain inhaled irritants is a causative factor in some cases. It is known that the inhalation of chromate dust or fumes may produce perforating ulcers of the nasal septum, and in 1890. Newman reported a large adenocaremona of the nases of a man aged 47 years who hid worked for 20 years in a chromate plant and who had a chiracteristic perforation of the septum. Stephens (1933) and Bridge (1939) refit to cases of nasal cancer in nickel workers. Neberle (1939) reported endomic nasal adeno caremomas in a flock of sheep—the animals were within the fume and dust zone.

carcinomas, the correct diagnosis of many of the cases so recorded will be plain It is of course now well recognized that most of the erstwhile 'mediastinal oat cell sarcomis' are secondary deposits of bronehial carcinoma (Barnard, Simpson, Bonser). It is still not sufficiently recognized that secondary growths in the pericardium pleura or cervical lymph glands may easily be mistaken for primary tumours (Chapter 10), and that other errors of pathological diagnosis are being made by those who are unaware of the structural versatility of bronehial cancer and the ease with which small primary growths may escape detection at necropsy (see Willis 1938, Turner and Wilhs, 1938).

(c) Modern diagnostic methods, especially radiography and bronchoscopy must have brought about, not only improved diagnosis of lung cancer, but an

increasing general acquaintance with the disease and its behaviour

(d) Pulmonary carcinoma will, of course, have shared in the general increase of cancer because of the increased proportion of old people in the population Comparison of city and recent necropsy series as regards the frequency of lung cancer have often failed to take account of the age compositions of the respective series. Since the disease is much commoner in men than in women, allowance must also be made for the sex ratios of necropsy series to be compared

(e) Of significance are the analyses of necropsy records made by Bonser (1928 and 1934) and by Passey and Holmes (1935) Bonser's analysis of the neeropsies during 41 years at Leeds, where an unusually high proportion of fatal cases were examined showed no increase in the incidence of intra-thoracic cancer when considered with respect either to the total number of necropsies, the total number of cancer cases, or the total number of admissions to hospital Passey and Holmes studied the incidence of intra thoracic cancer in the necropsy records of 16 major teaching hospitals in Great Britain, in 8 hospitals there was no evidence that this was increasing, in 3 the results were inconclusive, while in 5 institutions which did show an increase there were special circumstances which may have been responsible. Sitsen and Steiner also are among the many pathologists who deny that there is any satisfactory evidence of a real increase The suspicion is that where in the incidence of lung cancer during recent years such increase has appeared to have been conspicuous, there was formerly a low standard of accuracy of pathological diagnosis and that the standard has improved with the passage of time

For the foregoing reasons, comparisons of early and recent clinical or necropsy estimates of incidence, or comparisons of the findings in different countries or in different hospitals, must be quite unreliable. So much depends on the personal experience of the clinicians and pathologists concerned and current journals contain evidence enough that a uniformly high standard of diagnosis of this clusive disease has not yet been attained by either. Now that the properties of the disease are becoming better known, however, its true frequency and trend in a given community or institution might be ascertainable by meticulously careful and complete necropsies performed by skilled pathologists on all fatal cases over a period (probably 20 or 30 years) sufficient to obviate chance fluctual tions.

(2) Age incidence

Pulmonary earcinoma on the average affects rather younger people than most

CHAPTER 19

EPITHELIAL TUMOURS OF THE TRACHEA, BRONCHI AND LUNG

PULMONARY carcinoma, the main topic of this chapter is of special clinical FULMONARY CATCHIOMIA, the main topic of this chapter is of special clinical and pathological interest because of the frequent difficulties and errors of diagnosis and parmological interest occause of the frequent difficulties and errors of diagnosis which it occasions its variety of structure, its abundant metastases, its supposed which it occasions its variety of structure, its abundant metastases, its supposed increase in frequency, and the variety of its possible causative factors. Because of increase in frequency, and the variety of its possible causauve factors account the frequent misdagnosis of the disease, only fully proved necropsy records are the frequent misdiagnosis of the disease, only fully proved necropsy records are from the great number of necropsy from the great number of necropsy of any value for the analysis of its properties from the great number of necropsy which have been published those of the following writers will be found valuable—Fried (1925) 1927 and 1935) Duguid (1927) Kikuth (1925) Simpson (1928) 1927 and 1935) Duguid (1927) Kikuth (1925) Simpson (1928) 1927 and 1935) Duguid (1927) Kikuth (1928) 1927 and 1935 Duguid (1927) Kikuth (1928) 1927 and 1935 Duguid (1927) Kikuth (1928) 1927 and 1935 Duguid (1927) 1927 and 1937 Analysis (1927) 1927 A Valuable—Fried (1925) 1921 and 1935) Duguid (1921) Kikuth (1925) Simpson (1929) Karsner and Saphir (1930) Maxwell (1930), Bonser (1928 and 1934) (1929) Karsner and Saphir (1930) Monographs by Davidson (1930) and by Kraft (1934), Frissell and Knox (1937) Monographs by Davidson (1930) and by Krait (1934), Prissell and Anox (1931) Monographs by Davidson (1931) and by Simons (1937) give good outlines of the clinical aspects of the disease, and Simons (1931) give good outlines of the clinical aspects of the disease, and Chapter IV of Hueper's book (1942) contains an excellent account of possible Chapter IV of Hueper's book (1942) contains an excellent account of possible causative factors, with plentiful references. My own necropsy experience of 84 cases all of which were fully and carefully studied will be cited freely in this Bronchial adenoma and other relatively benign types of growth will be considered at the end of the chapter

FREQUENCY AGE SEX RACE AND SPECIES INCIDENCE

Whereas up to the second decade of this century, carcinoma of the lung was Whereas up to the second accade of this century, careinoma of the commonest regarded as a relatively rare disease. It is now recognized as one of the commonest (1) Frequency and its supposed increase regarded as a relatively rare disease it is now recognized as one of the continuous forms of cancer, accounting for between 5 and 15 per cent of cases of careinoma forms of cancer, accounting for between 2 and 13 per cent of cases of carcinoma in most recent necropsy series

Is the increase real or only apparent?

Attempts in most recent necropsy series as the mercase real of only apparent to answer this question have reached contradictory conclusions (Wahl Bonser) to answer this question have reached contradictory conclusions (want Passey and Holmes Kennaway and Kennaway Simons Hueper Passey and noimes Aennaway and Aennaway Shinons flueper Steiner,
Having read many of the contributions to the controversy and having surveyed Having read many of the contributions to the controversy and having surveyed my own experience of the diagnostic errors made in this disease my opinion is my own experience of the dragnosus errors made in this discuse my opinion is that it is not possible either to affirm or to deny that there has been a real increase

My reasons for this non committal opinion are briefly as follow reasons for this non committae opinion are onely as follow

(a) Chincal misdiagnoses even with all modern diagnostic facilities are tal Chaca misuragnoses even wan an mouern magnosuc facilities are still made in a high proportion of cases Between 1931 and 1944 I performed 84 suit made in a nigh proportion of cases of pulmonary careinoma all in a major general hospital, necropsies on cases of pulmonary carcinoma all in a major general nospital of these 35 (42 per cent) had been misdiagnosed 19 as some other kind of malignant of these 32142 per cent) had been amount more 12 as some other street manigname. Clearly then the mortality statistics diseases and 16 as non neoplastic diseases.

ung cancer are or autotous value

(b) Pathological misdragnoses are still made in not a few cases, and until the lus two decades they were very common Let anyone who doubts this look up of lung cancer are of dubious value ast two decades they were very common. Let anyone who doubts this book up some of the standard pathological journals for the later decades of the fineteenth century and study the many records of mediastinal sarcoma etc. In the light of what we enoma pleural or pericardial endothenoma etc. In the light of what we now know of the structure spread and misleading symptomatology of bronchial enoma

I studied a bronchial adenocarcinoma with metastases in the lungs and lymph glands in a 9-year-old English setter (Fig. 160)

POSSIBLE CAUSATIVE FACTORS

Every known inhaled substance and almost every known infection of the lungs has, by one writer or another, been claimed or suggested as a possible factor in the causation of pulmonary carcinoma. The subject is then confused



Fig 160 -- Adenocarcinoma of bronchus in a dog (× 120)

and confusing, and there is good reason for a succinct statement separating definitely established facts from a mass of speculation—even at the risk of seeming a little over dogmatic. The whole subject has been well reviewed by Hueper

(1) Infections

(i) Tuberculosis has often been described in association with carcinoma (Fried, 1935). In view of the frequency of pulmonary tuberculosis, this of course is inevitable, and no causative relationship can be deduced from such cases. Indeed, Rokitansky's opinion that cancer and tuberculosis were antagonistic has often been cited approvingly. However, there is no evidence to show that phthissis either predisposes to or protects from cancer of the lung.

(u) Influenza was at one time held to predispose to lung cancer, a suggestion which was devoid of any real basis and which now has few supporters

(in) Bronchitis appears frequently on pension claims as an alleged precursor of cancer but there is no satisfactory clinical, statistical or pathological evidence to suggest that it predisposes to cancer 'Bronchitis' is a very popular and very indefinite diagnosis and any chronic lung disease accompanied by a cough

other kinds of careinoma, the mean age of various series ranging between 45 and 55. The mean age of my 84 necropsy cases was 55, and their age distribution was as follows.

| Decade - | - | 3rd | 4th | 5th | 6th | 7th | 8th | 9th | Total |
|-----------------------------|---|-----|-----|-----|-----|----------|-----|-----|-----------|
| No of cases Percentage - | - | 1 | 5 | 15 | 31 | 22 26 | 9 | 1 | 84 100 |

The disease is not very uncommon in young people, the ages of my youngest cases were 29 30 and 33 Field and Quilliam described an anaplastic carenoma in a girl aged 4 and referred to Hirsch and Ryerson's case of adeno carenoma in a boy of 5 and to Beardsley's case of adenocarerinoma in an infant of 10 months. Dick and Miller saw a large solitary metastasis in the femur from a bronchalt carenoma in a girl of 9 years.

(3) Sex incidence

All series show a decided preponderance of males with an average of about 80 per cent (Sinions). My 84 necropsies comprised 70 men and 14 women, a ratio of 5 1. Since its very unlikely that there can be any real sexual difference between the lungs of males and females this striking difference in the sex incidence of lung cancer points strongly to the importance of extrinsic occupational or habitual factors in its causation.

(4) Racial incidence

Polmonary cancer is recorded from various non European peoples e.g. Malays Chinese, Japanese (Bonne) but of course there are no adequate figures for estimating its real incidence, and comparisons with the white races are not it present possible.

(5) Lung tumours in animals

Mice often develop single or multiple adenomas or adenocarenomas of the lungs. These turnours first fully described by Tyzzer, have been used extensively in experimental work as described in Sections I and VI of Chapter 4. In a large number of mice allowed to live their full span of life. Wells et al. (1941) found 2 per cent with carenoma of the lung metastases outside the lungs were present in a small proportion of cases and sarcoma like structure was seen in many of the turnours. Rats rarely get lung tumours and areas of bronchi extass with squamous metaplasia which are common in these numals must not be mistaken for careinoma. Feldman (1932) mentions infrequent examples of pulmonity careinoma in the horse ox dog cat sheep and kangaron himself (1931) described 3 lung tumours in sheep. Apperly described an adeno circinoma in a fowl. Nieberle and Cohrs (Fig. 158) depicted a large adenoma of a dogs lung and Poley and Taylor saw a pleomorphic cellular growth accompanied by hypertrophic osteo atthropathy in a young dog. Ruddwc, and

of such agents, absorption by other routes must also be considered. Tar, oil, soots, tobacco smoke and other smokes, must all be arraigned, but clearly, proof of either the culpability or mnocence of any particular material will not be easy to establish. Such proof will entail (a) demonstration of the presence of carcinogenic substances in the suspected material, (b) evidence that the material is inhalted or otherwise absorbed by exposed persons, and (c) evidence that habitually exposed persons do show an excessive meidence of lung cancer, and that this excessive meidence is reduced by eliminating the suspected risk. While the first step (a) has already been accomplished for many of the suspect materials, scarcely any of the evidence (b) or (c) has been obtained, and it will be very difficult to obtain

For example, suppose that tobacco smoking is an important cause of lung cancer and that it acts by producing chemical carcinogens which are inhaled It may be easy to identify the earcingens in tobacco smoke or far, but it may be difficult to prove that they are effectively inhaled, even more difficult to group patients correctly according to their present and past tobacco consumption, and probably impossible to prevail on any large group of men of homogeneous occupation to renounce smoking for life so that the ultimate incidence of lung cancer in them (proved by necropsy) may be compared with that of their smoking Comparisons of the smoking habits of victims of lung cancer with those of control eases obtained by careful questionnaires, like Muller's afford strong grounds for suspecting the carcinogenie results of smoking, but, however strongly suggestive, they cannot afford meontrovertible proof-especially in the eyes of smokers themselves ! Proof of the harmfulness of inhaled domestic and industrial soots and smokes or of dust from tarred roads, to which all persons in urban populations are almost equally exposed, will be even more difficult to secure

(4) Schneeberg and Joachimsthal and radio-active substances

The frequent occurrence of fatal lung disease in the miners of the Erzgebirge has been recognized for over four centuries, but only within recent years has this disease been clearly identified as bronehial careinoma. Hueper (p. 435) gives a full outline of the subject and Pirchin and Sikl's paper (1932) is a valuable source of information. The frequency of lung caneer in workers in the offending mines is very high about three quarters of the Schneeberg miners and nearly one half of the Jorchimsthal miners due of this disease. There is then no doubt of the operation of some highly potent occupational factor, probably an inhaled substance.

The air in the mines contains not only iron cobalt, nickel and silica duits, but also arsenic and radio active substances especially radon. Each of these has been incriminated as the eareinogenic agent by one writer or another, but the weight of the evidence fully outlined by Hueper, points to radon as the main factor. This is supported also by the fact that cancer of the lung has occurred in a number of laboratory workers handling radio active material. However experimental work has not yet verified the efficacy of inhaled radio active substances as a cause of lung cancer and until this has been done, a final decision must be deferred.

is apt to be so dubbed until its progress demands a more precise diagnosis. In many cases in which bronchitis "has appeared to precede the appearance of lung cancer by some months or years the symptoms were caused by the cancer from the beginning. There is no clinical evidence that bronchiectasis predisposes to carcinoma, but Womack and Graham, and Stewart and Allison found minute cancerous foci in bronchiectatic lungs.

(iv) Pneumonia —There is no evidence that pneumonia is ever a significant precursor of cancer Attacks of 'pneumonia due to bronchial obstruction, or of pleurisy' due to the same cause or to tumour invasion of the pleura, are common inaugural symptoms of bronchial carcinoma

(2) Pneumoconrosis

Hueper gives a full discussion of the contradictory opinions held regarding the possible importance of the several kinds of pneumoconiosis in the causation of lung cancer Silicosis is, of course sometimes seen in association with cancer, and has been thought by some workers (e.g. Klotz) to predi pose to this disease, but the evidence is inconclusive, and study of occupational groups exposed to silicosis does not suggest any special predisposition (Vorwald and Karr Kennaway and Kennaway and other references by Hueper)
Experimental results also have been inconclusive Vorwald and Karr failed to demonstrate any carcinogenic effect of inhaled silicates of various kinds in laboratory animals but Campbell's experiments (described in Chapter 4) showed an increased incidence of lung tumours in mice following inhalation of inorganic dusts containing silica Asbestosis has been reported in association with eareinoma in a few eases (Holleb and Angrist), and a causative relationship has been suggested because of the youth of several of the patients predominance of carcinomas of the squamous type, and multicentric origin apparently related to precancerous squamous metaplasia in some of them However the number of cases is yet too small to permit any definite conclusion to be drawn Siderosis accompanying lung cancer has been described in only a few cases, but the apparently excessive liability of metal grinders to pulmonary carcinoma and the results of Campbell's experiments with dusts containing iron oxide suggest a possible causative relationship Anthracosis has not been proved to be a causative factor. According to Kennaway and Kennaway, the registered deaths from lung cancer are fewer in coal miners than in the population generally. It has been suggested however that inhaled atmospheric soot the main source of the common anthracosis of city dwellers may be carcinogenic not because of its carbon content, but because it may contain carcinogenic hydrocarbons, a possibility now to be briefly discussed

(3) Caremogenic hydrocarbons

Experimental investigation outlined in Chapter 4 has shown that the incidence of lung tumours in mice can be markedly increased by the administration of carcinogenic hydrocarbons by inhalation or by subcutaneous intraperitioned or intravenous injections. The possibility must then be conceded that exposure of human beings to such substances may be a factor in the causation of lung cancer and that while inhalation is clearly the most likely mode of introduction

pathological and experimental research. There are strong grounds for believing that inhaled radio active substances can cause lung cancer, but experimental verification of this has yet to be made. Further study is required also on the possible careino genic properties of inhaled arsenic, chromates and nickel compounds. Neither trauma nor heredity plays any significant part in buman lung cancer.

SITE OF ORIGIN

(1) Side affected

As might be anticipated from the relative sizes of the two lungs, carcinoma of the lung occurs slightly more frequently on the right side than on the left Of 2,177 cases collected by Simons, the right lung was affected in 1,147, the left in 992, and both lungs in 38 cases. In my 84 necropsy cases, the origins of the tumours were in the right lung in 45 cases, in the left lung in 36, at the bifurcation of the trachea in 2 cases, and diffusely in both lungs in 1 case.

(2) Lobe affected

The lobar distribution of 649 tumours tabulated by Simons was right upper 169, right middle 70, right lower 119, left upper 179, left lower 112. My corresponding figures were 9, 3, 8, 9, 6, giving closely similar proportions. In many cases, of course, the tumours arise not in particular lobes, but in the main right or left bronchi or at the tracheal bifurcation, this applied to 42 of my 84 cases, and to 179 of Kilwih's 246 cases.

(3) Part of lung affected

At least three quarters of the tumours demonstrably arise in the large bronchi, either the main bronchi or the lobar bronchi in or near the hilar region. In my series the tumours arose in the main bronchi or tracheal bifurcation in 42 cases, in main lobar bronchi in 27 cases, in the periphery of the lung in 6 cases, diffusely and without recognizable local origin in 4 cases, while in 5 cases the tumours were so large that their origin could not be specified. Thus 69 tumours (82 per cent) demonstrably arose from large bronchi. Since the more peripheral tumours do not differ in structure or behaviour from those of obviously bronchial origin it is clear that all or nearly all pulmonary careinomas are bronchial careinomas. I have not seen a tumour, or a report of one, for which it seems necessity to postulate an alveolar origin, and, if such tumours do exist, I see no reason to suppose that they would differ in any special way from other pulmonary

(4) Apical carcinomas

These have been singled out for special description by elimicians, because of their proneness to involve the brachial and cervical sympathetic nerves (Pancoast Owen et al.) Pancoast's suggestion that these tumours have a special origin from branchial rests is quite baseless, the tumours are merely apical pulmonary carcinomas. Tumours of other kinds in the same region may of course produce similar symptoms.

(5) Arsenic

The earemogenic properties of arsenic for the skin naturally suggested that it might be the offending component of the dust in the Erzgebirge mines. There is some evidence too that workers with arsenic-containing sheep dips may be predisposed to lung cancer (Merewether), and it has also been suggested that the considerable quantities of arsenic present in tobacco smoke may be a danger in this respect (see annotation British Medical Journal 1946 1,94). Further statistical and experimental investigation is needed however, before it can be concluded that arsenic as a pulmonary carenopse.

(6) Chromates

Workers exposed to chromate dusts or fumes develop dermatitis, stomatitis rhinitis and bronchitis Over 25 cases of pulmonary eareinoma among chromate workers have been reported (references by Hueper, p. 410), but it is uncertain whether the responsible agents are the chromates themselves or some other substance.

(7) Nickel

Nickel workers often develop dermatitis and the volatile compound nickelcarbonyl produces acute poisoning accompanied by pilmonary oedema and haemorrhages. A high proportion of cases of cancer of the nasal passages and of the lungs has occurred in two Welsh nickel refineries (references by Hueper, p. 417).

(8) Trauma

Cases of earcinoma of the lung attributed to a blow on the chest or a penetrating wound are not unusual in insurance or war pension claims. There is no substantial statistical or pathological basis to support these, and when adequate data are available in such cases it is usually clear that the occurrence of injury prior to the onset of the tumour was purely fortuitous

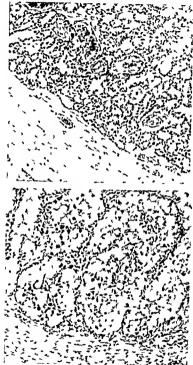
(9) Heredity, and developmental anomalies of the lung

While there is no doubt that different struns of mice differ markedly in the modence of lung tumours there is no evidence of any familial predisposition to lung cancer in human beings. Womack and Graham described cases of careinoma which they believed to have supervened on congenital bronchiectasis or cystic chinges but in my opinion the changes they observed were not developmental but were secondary to the tumours.

(10) Summary of possible causative factors

There is no satisfactory evidence that any of the common infections of the bronch or lungs predisposes to extensional. Silicosis is of doubtful causative importance and the evidence regarding the other forms of pneumoconiosis also is inconclusive. It is quite possible that the inhabition of careinogenic hydrocarbons or other substances in soots smokes and dusts including tobacco smoke is an important causative factor but proof of this will entail much more

structure appeared to be present in 65 tumours (77 per cent), while 19 tumours (23 per cent) showed heterogeneous or variable structure. The degree of structural



Figs 162 and 163—Acmar and signet ring cell adenocarcinoma from a woman aged 51, metastases in brain and adrenal respectively (× 120)

range in individual tumours is even greater than that indicated by the foregoing figures for the sections examined were only stray samples of parts of the growths, more thorough examination would certainly have disclosed variable structure in a larger proportion of cases.

Figs. 161-166 depict some of the main types of structure seen.

MICROSCOPICAL STRUCTURE AND ORIGIN

Most writers (e.g. Simons) distinguish at least three main types of pulmonary careinoma—adenocarcinoma, squamous cell careinoma and undifferentiated careinomas and more claborate classifications also distinguish oat celled spheroidal celled, mucoid, papillary and other types of growth. While these names all have descriptive value and while many pulmonary cancers consist predominantly sometimes exclusively of growth of a particular type, it must be emphasized that there is only one entity careinoma of the lung, that individual

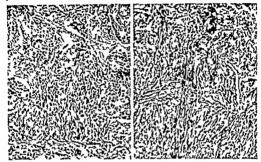


Fig. 161 - Spindle-celled carcinoma of bronchus from a man aged 73 (× 80)

tumours show various structural combinations, and that great pleomorphism is possible in one tumour. Review of the microscopical findings in my 84 necropsy cases (an average of 6 sections per case from different parts of the tumours, primary and secondary, were examined) showed the following variations of structure.

| Adenocarcinoma only (including acinar papillary | | |
|---|----|-------|
| mucoid and signet ring structure) | 16 | cases |
| Squamous carcinoma only | 12 | |
| Combined squamous and adenocarcinoma | 2 | : |
| Anaplastic carcinoma only (including out celled spindle | | • |
| celled spheroidal-celled and pleomorphic celled - | 37 | |
| Combined anaplastic and adenocarcinoma | 8 | : |
| Combined anaplastic and squamous careinoma | 5 | |
| Combined anaplastic squamous and adenocarcinoms - | 4 | , |

Thus anaplastic or undifferentiated structure was the most common at was present either alone or along with recognizably differentiated structures, in 54 tumours (64 per cent) Glandular structure alone or in combination was present in 30 tumours (36 per cent) Squamous structure was the least frequent, it was present alone or in combination in 23 tumours (27 per cent) Homogeneous

adenocarcinomas arising from peripheral bronchioles—is absurd Halpert and Pearson's view that all carcinomas of the lung arise from undifferentiated



Fig 165—Metastasis of mucoid adenocarcinoma in brain from a woman aged 29 A=general structure B=detail including two mitoses (x 80 and 375)

Oat-celled 'or spindle-celled structure (Barnard, Bonser Simpson Karsner and Saphir) is common in bronchial carenoma. It may form the whole or a large part of the tumour, or it may be found along with squamous-cell or glandular structures. The view adopted by some American writers that oat cell carenoma is essentially squamous celled is unacceptable, it is anaplastic bronchial carenoma, and is no more allied to squamous than to glandular epithelium.

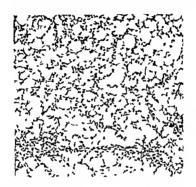


Fig. 164—From same case as Figs. 162 and 163, showing signet ring-cell structure in a metastasis in thyroid glatid. (× 120)

Certain other opinions regarding the structure and origin of lung cancers must be mentioned here to be deprecated. There has been much discussion as to whether these growths arise usually from the surface epithelium of the bronchia from the bronchial glands or from bronchiales or alveoli with attempts to interpret particular kinds of structure as denoting an origin from one or another of these sources. The pleomorphism of structure of many of the tumours shows plainly however that particular structural variants do not denote different specific origins. It is probable that all of the epithelial elements in the fields of origin of the tumours surface epithelia and glands alike participate in their formation just as enicerous change in the breast often affects large and small duets and acini smultaneously or successively. Extensive origin is particularly apparent in those cases of diffuse lung cancer sometimes bilateral with no distinct single focus in any of the affected bronch these cases are comparable with diffusely arising breast cancers biliary cancers or leather bottle cancers of the stomach

Geschickter and Denison's contention that lung cancers are divisible into two groups—hilar epidermoid careinomas arising from large bronchi and

larger nearly 5 centimetres in diameter in the central part of the left hemisphere. Careful search of all the viscera failed to detect any other growths, but the lungs were saved Microscopical study of the cerebral growths showed cystic adenocarmona of a type strongly suggesting a bronchial origin (Fig. 165). The lungs were then thoroughly searched and sections of several doubtful areas in the larger bronchis were prepared but no primary growth was found. Finally, on slicing the lungs into thin slabs a nodule of growth 4 millimetres in diameter was found in the long substance in the left upper lobe and this consisted of adenocaremoma resembling that in the cerebral metastases.

(2) Complications of cancer of the lung

These include bronchial occlusion, pulmonary collapse, bronchiectasis, pneumonia and abscess. Infection and cavitation of the tumours themselves sometimes occur (Atkin, Fishberg and Rubin). Pleurisy is frequent, due either to infective complications in the lung, or to cancerous involvement of the pleura, in the latter case commonly producing persistent effusion, often blood stained, and often containing identifiable tumour cells (Figs. 48 and 49). Osteo arthropathy is a rare remote effect of pulmonary cancer, but it may be the first symptom of the disease (Craig)

(3) Direct extensions of the growths

These often involve the mediastinum great veris, pericardium or heart. Gross invasion of the main pulmonary veris in the hilum of the lung is frequent and in some cases the intravenous growths project into the left atrium. Invasion of the superior veria cava or innominate veris is not unusual, and the growth in these veris may extend into the right atrium (Dana and McIntosh). The pulmonary arteries are often compressed or even obliterated by surrounding growth but they are invaded by tumour only rarely (Fig. 38). Invasion of the pericardial cavity, usually around the great vessels and base of the heart, may take place directly from the primary growth or from deposits in the mediastinal lymph glands. Epicardial extensions especially in the lymphatics, are not unusual, and they may reach the apex of the heart or may send prolongations into the myocardium. The heart may also suffer direct gross invasion the tumour replacing the myocardium over small or large areas (references, Willis, 1934, p. 259). Direct invasion of the oesophagus or of the vertebrae is uncommon. Apical tumours may involve the cervical sympathetic and the brachial plexus.

In many cases one or other of the various complications and extensions enumerated produce the first symptoms of disease, and often had to errors of diagnosis such as mechastinal tumour", "pleural tumour", "percardul tumour" pleurisy" "pneumona", "bronchiectasis", "cardine asthma', phthiss etc In 9 of my 84 necropsy cases, the final clinical diagnosis had

been of some non neoplastic intra thoracic disease

(4) The rate of growth and duration

In Chapter 8 reference was made to Eveleth and Wetzel's case in which following pneumonectomy, a small residue of bronchial carcinoma grew to 2,500 grammes in 88 days, and to a speumen of my own (Case II below) in which a metastrasis in the oral mucosa attained a weight of 12 grammes in 4 weeks On the other hand there occur tumours which he almost dormant for years, as

'reserve cells' in the bronchial epithelium is devoid of real foundation or meaning, it amounts to a self evident statement that the tumours arise from cells capable of multiplication, and the so called 'reserve cell carcinomas' are merely anaplastic

GROWTH COMPLICATIONS AND LOCAL SPREAD

In their size, rate of growth local spread and production of metastases, pulmonary carcinomas show the utmost diversity dimensions without producing remote metastases times almost microscopic yet produce large metastases some grow with unexampled rapidity others remain relatively small after several years duration Some form well defined solid masses of growth others produce more or less uniform diffuse thickening of the walls of the bronchi and others again produce still more diffuse il defined peribronchial infiltration of wide areas of a lung or of both lungs



Fig. 166 - Case 1 Metastasis of adenocarcinoma in brain (x 120)

(1) Minute carcinomas of the lung

These deserve special comment. Womack and Graham described three cases of bronchiectasis in which microscopic foct of abnormal epithelium identical in appearance with undifferentiated carcinoma were found. Stewart and Allisson saw a similar focus in a bronchiectatic lung. Turner and I described a case in which a small almost invisible carcinomatous area in a bronchus had produced fatal paraplegia from an extradural secondary growth. In the following case a minute primary growth produced fatal cerebral metastases.

Case I—A man aged 49 years underwent unsuccessful exploratory operation for crebral immour the symptoms of which had appeared re-entity and progressed rapidly. Neerops disclosed a well-defined partly cystic growths in the cerebrain the

(n) Extra thoracic lymph glands are frequently affected, usually by spread from cancerous thoracic glands, but sometimes from metastases in other organs. The most frequently involved are those of the upper abdominal, cervical and axillary groups. Cervical or axillary masses may be the first signs of disease and may cause misdiagnosis, as in a case which I recorded in my 1934 work (p. 433, Casc. 169).

(2) Metastases in scrous membranes

The pleura of course is frequently involved, dissemination in the pleural cavity has occurred in about one third of necropsy cases, e.g. in 25 of my 84 cases. In some cases, usually those with effusion many nodular metastases are present on both the visceral and parietal pleura in all parts of the cavity, in other caves there are only a few small nodules or plaques of growth at sits other than the region of primary pleural invasion. The pericardium is cancerous in about one quarter of fatal cases, and the peritoneum in about 10 per cent of cases. Most supposedly primary tumours of the pleura or pericardium are really secondary to undetected bronchial carcinomas (see Chapter 10, and Willis, 1934, p. 77, and 1938).

(3) Blood-borne metastases

Metastasis by the blood stream is demonstrable in about three quarters of fatal cases, e.g. in 61 of my 84 cases. The organs most frequently affected are the liver, adrenals, central nervous system, bones, kidneys and lungs themselves but no organ is exempt.

(1) The liver contains metastases in neurly one half of fital cases e.g. in 32, 39 and 47 per cent respectively in Simpson s, Kraft's and my own series. Hepatic enlargement may be the first sign of disease and may lead to a false diagnosis of

gastrie or other abdominal cancer, as in 3 cases in my 1941 paper

(ii) The adrenals show metastases in a surprisingly high proportion of necropsies, e.g. in 30, 32, 34, 36 and 40 per cent respectively in Simpson's, Bonser's, Kratt's Glomset's and my series. In most cases these metastases are multiple and bilateral and are usually situated in the medulla. It is not unusual for the adrenals to be the only site of distant metastases, or for the brain and adrenals to be the only sites. Cerebral and adrenal metastases frequently coexist this applied to 11 of my crises, i.e. to one third of the cases with adrenal deposits and to nearly two thirds of the cases with cerebral deposits. The adrenal growths rarely attain a large size or produce any symptoms.

(ii) The central nerrous sistem, usually the brain, contains metastases in about one quarter or one third of fatal cases, e.g. in 31 per cent according to Dosquet, 41 per cent according to Fried and Buckley and 21 per cent in way series. In many cases primary cerebral disease is simulated and a relatively symptomiess pulmonary growth is overlooked. Thus, in 11 of Simpson s 19 cases with cerebral metastases, the clinical diagnoses were erroneous, and in 7 of my 18 necropsy cases with metastases in the brain primary cerebral disease had been diagnosed. Elsewhere (1934, p. 188) I have referred to many other examples of such musdiagnosis. In all cases diagnosed as "cerebral timeour discontinual controlled."

nd in all cases of cerebral disease of obscure nature, careful radiographic

in my case reported in 1938, in which there was good evidence that a small unsuspected bronchial careinoma found at necropsy had been present for at least 31 years. Goldman reviewed 11 eases of lung cancer with symptoms for longer than 2 years the durations ranging from 28 to 244 months. 10 of the tuniours were of epidermoid type.

While the average symptomatic duration of lung cancer is only a few months this is no guide whatever to the real duration of the tumours. Many of the primary growths remain symptomless and unsuspected during a large part or the whole of their course, and many others are found at necropsy to be of a size and structure clearly showing a duration far longer than that of the symptoms they have produced In most cases the real duration of lung cancer cannot be determined even approximately and all estimates of average duration based on symptoms are bound to be decided underestimates. This is an important point in considering the alleged causative influence of recent infection or trauma.

(5) Cancer cells in sputum

These have been identified by many workers (references in annotation British Medical Journal 1947 1 20) but I believe that the diagnostic rehability of sputum examination has been over estimated. Only a minority of tumours produce free clumps of tumour cells recognizable with certainty, the recognition of isolated tumour cells amongst the various non neophystic cells in sputum is rarely possible. Diagnosis from sputum examination alone, unverified by biopsy or necropsy should be viewed with great caution.

(6) Simulation of bronchial carcinoma by secondary growths

It is important for both bronchoscopist and pathologist to recognize that secondary growths in the lung sometimes involve the bronchial walls and simulate primary growths in appearance This may occur from metastatic carcinomas sarcomas or melanomas (King and Castleman) and I have observed it also from invasion of the main bronchial walls by hitar Hodgkin's disease and lympho sarcoma

METASTASIS

With no other neoplasm is a knowledge of metastasis more important to the clinician than with pulmonary carcinoma. This tumour metastasizes with great frequency often widely and often at ni carly stage while the primary growth is still small and symptomiess. More diagnostic mistakes due to metastases are made in this disease than in any other.

(1) Metastases in lymph glands

(i) The hilar or mediastinal glands contain tumour deposits in a high proportion of fixal cases (e.g. in 104 of Simpson s 139 cases (75 per cent) and in 76 of my 84 cases (94 per cent). These often ittain large sizes frequently becoming much bulkier than the primary growth. Infiltrating tumours of the hilum commonly coalesce with the lymph nodel deposits or on the other hand, they may incorporate unriffected lymph nodes.

Case II —A man of 70 years had noticed two rapidly growing masses in his mouth for 4 weeks. Examination showed well defined projecting slightly ulcerated purplish masses springing from the gums of the posterior molar regions of the lower jaw one on each side. The larger tumour on the left side was excised, it was an oxid mass 3 centimeters in main diameter. 12 grammes in weight and clothed by stretched partly denuded mucous membrane. Microscopically it showed anaplastic carcinoma suggesting a pulmonary origin. A skiagrams revealed a large shadow in the right lower lobe some distance out from the fulum. The remaining gingival metastasis continued to increase rapidly ulcerated, and the patient died a few weeks later.

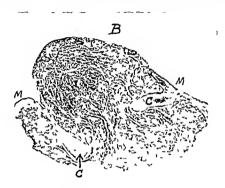


Fig. 168—Case IV Bronchial adenoma B = lumen of bronchus M = mucosa C = bronchial cartilages enveloped by growth (×6)

Case III—For 6 months a middle aged man had suffered from an ulcerated growth in the floor of the mouth. This was regarded as a carcinoma and was treated by radium with good result. There then developed a large right sided pleural effusion which was aspirated. The fluid was slightly blood stained and somewhat turbid and mucinous and examination revealed many clumps of fumour cells including signet ring cells distended by droplets of mucin (Fig. 48). Skiagrams showed a large mass in the right long Necrops; revealed a huge mucoord admocaracinoma replacing most of the right lung with metastases in the thoracic lymph glands one kidney and both adrenals. There was a scarred area in the floor of the mouth but no residual tumour. It is of course possible that it was a metastasis of the lung tumour which must already have been well advanced at the time the oral growth first appeared.

Other unusual metastatic sites included in my series were myocardium, thyroid, pancreas, ovaries spleen pituitary gland, mucous membrane of gall bladder, prostate and testis, and references to other examples are given in Chapter 29 of my 1934 work.

BRONCHIAL ADENOMA"

The tumour now commonly designated bronchial 'adenoma' was first described by H Mueller in 1882 In 1931 Geipel reviewed 6 reported cases

examination of the lungs should be a routine part of the chinical examination, before any surgical intervention is contemplated. Adherence to this practice would obviste many useless operations

The metastases of pulmonary carcinoma have a distribution similar to that of metastatic growths in general in the nervous system (1934, pp. 353.5 and 366-9)

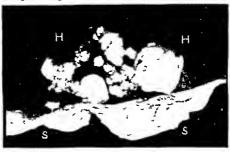


Fig. 167—Masses of metastatic growth projecting into hydrocele cavity (HH) from the sac wall (SS) (Slightly reduced)

The metastases are more often multiple than single are situated about equally often on the two sides and affect the cerebrum cerebellum brain stem and spinal cord in that order of frequency. Diffuse or nodular dissemination in the lepto meninges is usually secondary to metastatic deposits in the brain or choroid plexus as in cases described by Ginsberg Putscaar Fried and Shennan but it is possible that in occasional cases the meninges may be infected by direct sprend from the thorax into the theca as suggested by Rehn Miller and Alpers and Smith. Massive extradural extensions through the intervertebral foramina may also produce compression of the thoracie part of the spinal cord (Turner and Willis). The papers of Elkington Minkowski Globus and Meltzer and Birker contain instructive examples of metastatic tumours of the brain from pulmonary carcinoma.

(n) Skeletal metastases are present in about one-quarter of fatal cases and have often been mistaken for primary tunnours or other bone diseases (references 1934 p 189 and Case 136 p 433). Cosin described a man of 25 in whom metastases in many bones from an oat-cell caremoma produced punched out areas radiographically resembling myelomatosis, accompanied by anaemia thrombocytopenia and splenomegaly.

(i) Other sites metastases in which have caused difficulties of diagnosis or have caused early symptoms include the eyes (Hudson) the skin (see Case No 263 1934 p 433) intestines (Barnard and Elhott) a hydrocele sic (Willis, 1938 and Fig 167) the tongue (Fitzwilliams) and the oral mucosa as in the following two cases

post operative haemorrhage into the pleural eavity Operation Specimen—A lobulated well defined firm white growth 5 centimetres in main diameter projected into the greatly dilated lobar bronchus and also into the surrounding tissues—it had been cut across in its promate.

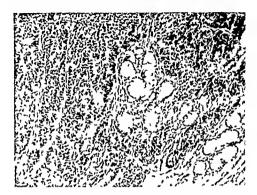


Fig. 170 —Case IV Mucous glands included in bronchial adenoma (x 120



Fig 171 - Case V Bronchial adenoma (× 120)

part where it had involved the main bronchus. The rest of the lung showed bronchiectasis collapse and infection. Histology (Fig. 171)—Uniform solid trabecular structure but with some glandular acini slight marginal infiltration of surrounding ussues present in

added 2 typical examples, and proposed to distinguish them from the usual bronchial carcinomas by calling them being basal-cell carcinomas." Increasing recognition of the tumours and of their favourable outlook, following adequate surgical removal led to their separation as a distinct group. Hamperl's description of 9 cases (1937) includes some excellent photomicrographs, and Foster Carter's admirable review of 70 cases (1941) is the best general account.

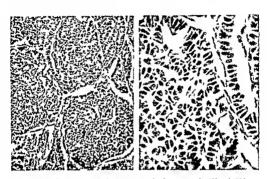


Fig. 169 - Case IV Bronchial adenoma details of structure (> 100 and 400)

(1) Personally studied specimens

I have studied 6 examples of these tumouts all from young adults between the ages of 18 and 40 years all with long histories from 2 to 16 years in duration and all with characteristic gross and microscopic structure (Figs. 168 175). I record the following three examples

Case IV—History—Right lower lobectomy successfully performed by Mr. C. J. O. Brown of Melbourne on a man aged 40 years following a history of cough and haemophysis for 2 years. Gross Sinecture—Main lower lobe bronchus the site of a well-defined white tumour 3 centimetres in diameter projecting into the bronchus and also expanding into the surrounding lung tissue, with bronchial cartilages visibly included in the tumour (Fig. 168). Remainder of lobe shows obstructive bronchiectasis collapse and infection Historicy (Figs. 169 and 170)—Uniform structure of Solid epithelial masses and trabeculae but with formation of distinct glandular tubules in places. Distinct infilitation of the bronchial mucosa and of the extra bronchial tissues present at parts of the growth margins. Some of the bronchial mucosa glands included within the tumour show apparent direct transition from glands to tumour (Fig. 170). Some markedly enlarged hilar lymph glands showed inflammatory changes only

Care 1 — Hattury - A woman assed 39 years had had attacks of pneumonia at the ages of 13 and 16 and since the age of 23 (i.e. for 16 years) had had frequent haemorphises. Tuberculosis had been suspected but bacilli were not found and her general health termained good. Investigation disclosed a growth in the right lower lobe bronchus and Mr. C. J. O. Brown performed lobections with difficulty. Death occurred from

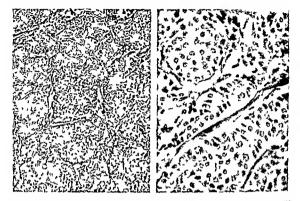


Fig. 173 —Bronchial adenoma from a man aged 28 solid trabecular structure (x 100 and 400)

- (11) Age medence—The tumours develop much earlier in life than most bronchial carcinomas. In those reviewed by Foster Carter, the muan age of onset of symptoms was 28, 70 per cent had given symptoms in the third and fourth decades, and the age range was 11 to 66 years. The symptomatic duration was often very long, the average duration prior to diagnosis being about 5 years, the longest recorded duration being 40 years and in Foster Carter's own series 23 years. In my Case V, the tumour had certainly been present for 16 and possibly 32 years in some of the recorded cases the tumour has been observed to remain stationary for several years.
- (iii) Sev incidence Unlike careinoma bronchial "adenoma' affects the sexes about equility, 62 per cent of the patients reviewed by Foster Carter were females.
- (1) Site—Bronehial 'adenomy' is invariably situated in a large bronehus close to the fulum, never in the periphery of the lung. Right sided tumours are more frequent than left sided, and the favourite situation is in the right lower lobe bronehus.
- (1) Causative factors—These are unknown that the occupational factors which certainly play a part in the causation of bronchial carcinoma are not important as regards "adenoma", and Foster Carter's putients had no distinctive occupations.

(3) Structure and growth

(a) Gross appearance

The tumours are well defined, firm uniform rounded or lobulated masses, averaging 3 or 4 centimetres in diameter, projecting into the bronchial lumen

places stroma contains scattered spicules of bone Enlarged bronchial lymph glands clear of growth Necropsy showed a small part of the growth left in the main bronchus but no metistases

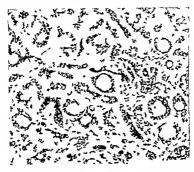


Fig 172 - Case VI Tumour of traches (x 120)

Case VI - History - A woman of 24 years had had several haemoptyses during the previous 3 years. I year of which she spent in a suberculosis sanatorium sputurn examinations showed no bacilli and skiagrams of lungs showed no abnormalities Bronchoscopy showed a soft readily bleeding mass of growth partly occupying the traches at the level of the manubrum Histology (Fig. 172)-Pieces of this growth showed well-differentiated branching glandular tubules solid epithelial cords and cribulorm clumps resembling those often present in salivary tumours set in plentiful vascular partly hyalinized stroma. Many of the glandular components of the growth were in gentle continuity with glands of the tracheal mucosa Later Progress-Deep Y ray therapy was instituted but 6 months later the patient had lost condition pain and neakness of the left arm had developed and a small subcutaneous nodule had appeared on the back. This was excised and showed an active carcinomatous growth composed mainly of large clumps of anaplastic epithelium with many mitoses but with areas of narrow trabecular structure re embling that of the tracheal tumour Small patches of bone were present in the stroma. Skiagrams showed partial destruction and collapse of the first dorsal scriebra. The patient died a month later. Necrops -- A mass of growth springing from the posterior wall nearly filled the trachea from about 5 centimetres below the glottis to just above the bifurcation. Multiple metastatic growths were present in both lungs pleura mediastinal lymph glands liver and seriebrae Microscopically these generally resembled the subcutaneous metastasis

(2) Incidence and causation

(i) Frequency—Bronchial adenomas appear to constitute about 5 per cent of bronchial tumours My 6 specimens came under observation during the same period in which my 84 necropsies on cases of bronchial carcinoma were performed "adenomas" as well as the salivary tumours arise specifically from "onkocytes" Nor is there any substantial evidence to sustain Womaek and Graham's ominion

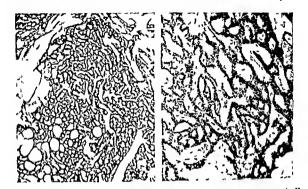


Fig. 175 —Bronchial adenoma from a man aged 32 retiform trabecular structure (x 50 and 120)

that they are 'mixed' tumours of developmental origin, the occasional presence of bone or eartilage in them is readily attributable to metaplasia or to the inclusion of parts of bronehial eartilages

(d) Malignancy

The tumours grow mainly expansively, but restricted infiltration of the submucous tissues or lung is often to be seen at their margins. It is usually stated that metastasis does not occur, but Adams et al have reported metasta sizing growths not sharply separable from the "adenomas", and my Case VI is a striking instance of the same kind. Hence, while admitting that the name 'adenoma" is justified by the frequently benign behaviour of the tumours, we must be prepared to see occasional members of the group transgress the bounds of innocence, just as with the pleomorphic salivary growths. The prevalent opinion that the group is sharply distinct from carcinoma and invariably benign 15 uninstified

OTHER BENIGN EPITHELIAL TUMOURS

After segregation of the distinctive group of bronchial "adenomas', there is left a rather miscellaneous assortment of rare benign bronchial and pulmonary tumours variously recorded as papillomas, "fibro adenomas, "hamartomas, chondromas", and "mixed tumours some examples of these will explain their structure and possible relationships

The so called 'chondromas of the lung, well described by Moller, and by

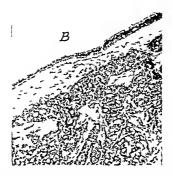


Fig. 174 —Bronchial adenoma from a girl aged 18 B = lumen of bronchus note intact mucosa (/ 80)

but usually covered by an intact layer of distended mucosa. In many cases the tumour is like an iceberg in that its bulkiest part lies outside the bronchus in the surrounding hilar or lung tissue and its presenting part seen bronchoscopically is its smaller part. Apart from cough and haemoptysis, the main symptoms are those produced by bronchial obstruction with collapse and infection of the lung

(b) Microscopic structure

This differs from tumour to tumour but is usually very uniform throughout each individual tumour. About one third of the specimens show well differentiated glandular acini or tubules usually without but sometimes with mucoid secretion but the remaining two thirds consist mainly of solid epithelial columns or masses with only scattered signs of glandular orientation of the cells. The polyhedral, wedge shaped or elongated cells are uniform in size and structure, without signs of disorderly growth and with only occasional mitotic figures. The vascular fibrous stroma is usually scanty but sometimes more plentiful and hyaline sometimes it contains areas of metaplastic bone as in Womack and Graham's case and 3 of my eases including V and VI above

(c) Origin

There is I think hitle room for doubt that the tumours arise from the mucous and mixed glands of the bronchial wall and that they are as Foster Carter suggests comparable with the more being of the pleomorphic salivary tumours. They resemble those tumours in their circumscription slow growth and variable structure, they differ from them in rarely secreting much mucus and in their more regular beingnity. My Cases IV and VI showed evidence of direct continuity of the growth with the mucori glands. I see nothing to favour the rice, suggested by Hamperl and supported by Stout that the bronchial

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intra canalicular fibro adenomas of the breast, but their stroma consisted in one case of fibrous and adipose tissue and in the other of fibrous tissue only and was devoid of cartilage. Had their stroma chondrified, their structure would have been identical with that of the "chondromas"

Harris and Schattenberg reported two peculiar "anlagen tumours" in the lungs of new born infants. In one case an entire lobe was replaced by a mass consisting of branching tubules lined by columnar cells, and separated by scanty stroma containing islands of cartilage. In the other case the left upper lobe contained an irregular vascular mass with the structure of embryonic lung tissue. Whether these masses were true tumours, is, I think doubtful, they were probably developmental anomalies without powers of independent growth

In the lungs of a woman aged 73, Richardson found multiple small nodules composed of glandular structures lined by mucoid columnar epithelium. No primary tumour was found elsewhere, and the condition was diagnosed as multi-focal "adenomatosis" of the lung

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Goldsworthy, are not simple chondromas but always contain bronchial epithelium in clefts between the cartilaginous masses and may include also mucoid, adipose,



Fig. 176—Case III Chondroma of lung E = epithehal closs C = chondrification in fibrous issue $F = \text{fat cells in fibro-cartilagenous ussue } (\times 80)$

fibrous lymphoid and muscular tissue. Moller who for this reason called them mixed tumours described a typical specimen from a man aged 44 and showed that the structure was exactly comparable with that of an intra canalicular fibro adenoma of the breast consisting of a papillary growth of the bronchial formation in the stroma was brought about by a specific inductive effect of the profiferating epithelium on the connective tissue of coldsworthy observed similar structural relationships in a specimen from a man aged 58 which he designated

hamartoma chondromatosum However I think it unnecessary to postulate any developmental anomaly as the origin of these tumours the structure of which can readily be accounted for in the way suggested by Möller A personally studied specimen may be briefly described

Care III —At necropsy on a man of 66 years who died of carcinoma of the colon an incidental finding was a solitary well defined firm nodule 1 centimetre in diameter situated in the middle of the lower lobe of the left lung. This was at first thought to be a metastate growth with some muoned change but microscopical study showed it to consist of irregular masses of fibro-cartilage numgled with some adopose issue, partly separated by elefts lined by cubical or columnar epithelium which was clitated in places (Fig. 176). Much of the stroma was fibroblasm, and all transitions from fibrous tissue to cartilage could be traced.

The two fibro adenomas of the lung described by Scarff and Gowar were probably related to the chondromas. These tumours found in men 24 and 66 years old respectively, also showed a structure like that of the

intra canalicular fibro adenomas of the breast, but their stroma consisted in one case of fibrous and adipose tissue and in the other of fibrous tissue only and was devoid of cartilage. Had their stroma chondrified, their structure would have been identical with that of the "chondromas"

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eases Soutiar's ocsophagoscopic examination of 98 cases showed the upper limits of the growths to be in the upper third (less than 10 inches from the teeth) in 16 cases, in the middle third (10 to 14 inches from teeth) in 69 cases, and in the lower third (15 inches or more from teeth) in 13 cases. The upper limits of 436 growths in the Cancer Campuign series were—upper part 52, middle part 204, lower part 180. At necropsy many of the tumours are so extensive that their precise level of origin is uncertain. A prevalent idea that the narrow regions of the ocsophagus are thereby predisposed to cancer is very dubious.

CAUSATIVE FACTORS

Although it is very probable that dietetic and dental factors—alcohol, tobacco, insufficient in istiection, hot foods, foods containing chemical careinogens, or foreign bodies—are largely responsible for cancer of the gullet, it is naturally difficult to prove the culpribility of any particular factor. Careful inquities into the dietetic habits of patients with ocsophageal and gastric cancer, like that recorded by Craver, but in much larger series of cases, are needed. The problem is more fully discussed in the next chanter.

Schaer referred to reported cases of oesophageal caneer associated with leucoplakia diverticula, ulcerative and infirmmatory lesions and compression of the organ by ancurysms or bony projections from spondylius. Schaer himself examined 237 oesophage for possibly pre-cancerous lesions, he concluded that leucoplakin is very commonly present in the adult organ and cannot be regarded as an important pre cancerous lesion, that suspicious epithelial proliferation or definite carcinoma is sometimes seen in or near diverticula, and that other inflam matory lesions also may occasionally precede cancer. However, the evidence on these matters seems to me to be inconclusive. The association of feucoplakia with cancer was studied also by Sharp. The Plummer-Vimson syndrome as a precursor of oesophageal cancer (see Ahlbom's findings cited in Chapter 15) probably applies only to post circoid cancer, but further investigation is needed

STRUCTURE

Little need be said of this With rare exceptions the tumours are epidermoid caretinomes resembling those of the oral cavity or pharynx, they vary much in degree of differentiation from highly cornifying tumours to disorderly anaplastic growths devoid of recognizable epidermoid characters. Lympho-epitheliomas do not occur. Tumours of basal cell type are said to occur, but I have never seen an example

Rare odenocorcinomas, sometimes mucoid in type have been reported by Franke and by Kaufmann Some writers have suggested that these may arise of the small islands of gistric mucosa which are common in the upper part of the oesophagus, but tumours of this origin would not be distinguishable from those arising in the glands of the oesophagus itself

LOCAL EXTENSION

Many tumours extend annularly and produce stenosis, others spread long tudinally, forming an oval ulcer, plateau or fungus. They soon invade and replace

CHAPTER 20

CARCINOMA OF THE OESOPHAGUS

CARCINOMA is the only common tumour of the oesophagus adenomas and papillomas are very rare. Simple submucous cysts hard by squamous stratified enthelium are not uncommon but are seldom large enough to cause symptoms.

AGE SEX RACE AND SPECIES INCIDENCE

(1) Age

The age distribution curve of cases of carcinoma of the oesophagus has its peak late in the sixth decade, or in some series in the seventh More than three-quarters of the tumours appear in people over 50 years old. The mean age of Pack and Le Pevre's senes was 57, and of those in the British Empire Cancer Campaign report (1942) 65 years. The mean age at death of my 35 necropsy cases was 67. The disease is rare und r 40 years of age but has been seen at 21 and 19 years (Kaufmann, klein)

(2) Sex

The disease is much commoner in men than in women, the combined figures of Kaufmann, Souttar Graham and Ballon and my own necropsy cases show that 37 per cent of 471 patients were men a percentage the same as in klein's series. Post ericoid carcinoma, considered in Chapter 15 is much commoner in women.

(3) Race

Because of the considerable proportion of diagnostic errors (see Chapter 5), no accurate racial comparisons are possible for ocsophageal cancer. The disease is common in all European races, and has often been reported in Negroes Indians, Chinese and other Eastern peoples.

(4) Species

Moschkowitz and Sprinz reporting a cateinoma of the oesophagus in an antelope, cited other rare records of this disease in cats horses, bovines, a primate a fowl a mule, a sheep and a turkey

SITE

Reported series show wide differences in the distribution of the tumours Graham and Ballon cited the following range of differences recorded—in the upper third of the organ 12 to 27 per cent of the tumours in the middle third 30 to 49 per cent in the lower third 26 to 63 per cent. Alein reviewed a veral reported series which showed the middle third to be the most frequent site. The states in Kaufminn's cases were upper third 31, middle third 61 lower third 84.

upper oesophagus may produce bulky cervical tumours as the first or main symptoms as in cases described by Kaufmann, Erdheim, and Davies Caru nomas of the lower half of the oesophagus frequently produce metastess in the Jupper abdominal, as well as the mediastinal, lymph glands Secondary invasion of the stomach from deposits in the glands around its cardiac end may simulate the appearance of an independent primary gastric growth (Borrmann)

(2) Blood borne metastases

These are present in about one-third of fatal cases (Klein Kaufmann Willis) the commonest sites being the liver and lungs—In my 2 necropsy cases with cerebral metastases these had very similar situations, in one case there was a single nodule in the left occipital cortex, and in the other case cach occipital pole contained a metastatic nodule. In cases recorded by Franke and Souttar, symptom less primary growths had produced multiple cerebral metastases, simulating cerebral tumour.

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ev. vary much in

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ev varv much in rderly anaplastic pho-epitheliomas I have never seen the muscle coat and the peri ocsophageal tissues. Ulceration of soft growths leads to ragged sloughing and suppuration in them. Outcrop satellite growths in the neighbouring ocsophageal or gastne mucosa are not unusual, although these may appear to be separate from the main mass microscopical study usually shows plainly that they have resulted from submucosal extensions in lymphatics or blood vessels. Occasionally however, multifocal tumour formation appears to have taken place and certainly some early careinomas show clear evidence of tumour genesis still in progress at their margins (Fig. 177).

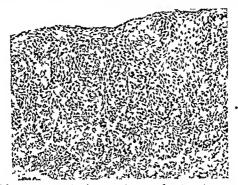


Fig. 177—Epithelium marginal to a large ulcerated carcinoma of oesophagus, showing cancerous change In situ, comparable with Bowen's disease of the skin. (× 120)

Invasion or perforation of surrounding organs the lungs bronch trachea aorta heart pleural cavity or spine is very frequent. Invasion of lungs or bronchi leads to septic pneumonia a common cause of death from ocsophageal cancer Invasive complications may occur from symptomless or unsuspected growths e.g. Kaufminn saw fatal paraplega from spinal invasion and in one of my necropsy cases an upparently healthy man had died suddenly from perforation of the aorta. Invasion of the pericardium or heart is exemplified by the cases of Hebb and Geipel, the latter saw direct perforation of the growth into the left atrum. Leichtenstern saw invasion of the avgros vein and intravascular growth into the superior vena cava and right chambers of the heart.

METASTASIS

(1) Metastases in lymph glands

These often occur early and are present in over two thirds of necropsy cases (Klein Clayton Willis) Like oral and pharyngeal growths those of the

must have improved diagnosis of recent years, and an apparent trend in the frequency of gastric cancer might be only a trend in the proportion of cases identified as such

(2) Age incidence

In most series the greatest number of cases occurs in the sixth decade Konjetzny gives the mean age as 54 years, which was the same as in Pack and Le Fevre's hospital series The mean age of Poscharissky's 500 necropsy cases in Moscow was 51 years, and of my 227 necropsy cases in Victoria 62 years. The disease is rare under 30, but Kaufmann mentions patients of 21 18 and 9 years, and proven cases of 13, 14 and 15 years were reported by Moore, Ness and Teacher, and Land

(3) Sex incidence

In nearly all countries the mortality rates from gastric cancer are decidedly higher for men than for women. The Registrar General's figures for England and Wales, 1930 32, show 18,876 male deaths and 9,243 female deaths from this cause, a ratio of 2 to 1. The greater hability of men to the disease is borne out also by surgical and necropsy records. Kaufmann recorded 394 necropsies on males and 227 on females, Poscharissky, 345 and 155 respectively, and my series 157 and 70. The sex ratio of these figures combined is almost exactly 2 to 1. Pack and Le Fevre's clinical series showed a ratio of 22 to 1.

(4) Social class and gastric carcinoma

Cancer of the stomach was one of those tumours which according to the Registrar-General's figures, showed a decided class gradient, people in the un skilled classes showing the higher medence. The standardized mortality ratios in the 5 descending social classes were 59, 84, 98, 108 and 124 for males, and 55, 78, 105 104 and 120 for married females. That the wives of men in the lower social classes share with their husbands the increased highlity to gastric cancer, suggests that the causature factors are connected more with general economic circumstances, home life or diet than with occupation

SITES OF GASTRIC CARCINOMAS

The situations of the tumours in Stewart's (1931), Poscharissky's and my own series of necropsics were as follow

| 1 | | | | | | | |
|--|-------------|--|-----------------------------|------------------------------|-----------------------------|--|--|
| Site | | | Stewart | Poscharissky | Willis | Total | |
| Pylorus and antru Lesser curvature Cardia region Rest of organ Whole stomach | m - - | | 155 40 37 26 21 | 194 170 45 52 39 | 125 52 21 11 18 | 474 = 47,0 262 = 26% 103 = 10% 89 = 9% 78 = 8% | |
| | | | 279 | 500 | 227 | 1 006 | |

CHAPTER 21

CARCINOMA OF THE STOMACH

CARCINOMA is by far the commonest epithelial tumour of the stomach Benign epithelial tumours are relatively infrequent and since carcinoma often super venes in them they will be discussed with the precursors of carcinoma Konjetzny s admirable monograph (1938) gives a good account of the pathology of gastric carcinoma

FREQUENCY AGE AND SEX INCIDENCE

- (1) Frequency and race incidence
- (a) Mortality records

These show that cancer of the stomach is one of the commonest tumours in all European peoples but its frequency as a registered cause of death differs markedly in different countries. The high proportion of errors in the clinical diagnosis of gastric cancer (see Chapter 5) limits the reliability of the mortality figures in comparing the frequency of the disease in different countries but the differences recorded are too great to be accounted for wholly by errors of registra tion. In Great Britain and in Australia about one quarter of cancer deaths are recorded as due to cancer of the stomach in Scandinavia Holland Bayaria. Switzerland and Czechoslovakia more than one half of them the highest proportion being Gzechoslovakia s 66 per cent in USA the proportion is about spetzny and Hoffman Cramer and the Registrar (1975) hapter 5) Gastrie cancer is also one of the commonest timese accounting for 75 per cent of recorded cancer

recent in females It is also very common in the Fig. 177 - Epithelium margina uhans (Hoffman) but is decidedly less common in change in situ comparable, also probably in Indians

Invasion or periora gical records and also its different and a least, pleural cav minimines of my 1060 nectopsy cases of carcinoma leads to septic pneumonth equil numbers of male and female beds (Table V Invasive complications it was the primary site in 227 cases (21 per cent) these e.g. kaufmann saw fat 5 males (25 per cent) and 70 out of 425 females (16 per necropsy cases an pa and necropsy series from those European countries mortality figures for gustric cancer show correspondingly Hebb and Gerr to 70 per cent) for this disease atrium Leich

quency of gastric careinoma cannot be estimated reliably into the supe able 1 of Chapter 5 shows that in a large general hospital icians to diagnose this disease in about 30 per cent of cases isated for by the number of cases erroneously diagnosed

(I) Metastases in stomach But it is not justifiable to assume from this that These often oc and negative misdiagnoses will cancel each other out Vien Clayton's such as radiography test meal examinations and gastroscopy

(1) Gastric ulceration as a precursor of cancer

The vexed question of the frequency of encerous change in chronic ulcers and the proportion of cancers which arise in previous ulcers has been fully discussed by Dible, Orator, Stewart, Newcomb and Konjetzny The following conclusions can I think, be safely made (a) Routine microscopical study of the margins of chronic gastric ulcers of prolonged history and typical naked-eve appearance reveals evidence of genuine early cancerous change very rarely indeed (b) Clear examples of localized careinoma at one part of the margin of an other wise simple chronic ulcer, and examples of a ring of carcinoma encucling an area of ulceration with a cancer free fibrous base, are uncommon number of cancer specimens encountered which show good evidence of preceding ulceration is small compared with the total number of gastric ulcers encountered The proportion of presumed ulcer cancers in Stewart's series of 358 operation specimens was 6 per cent in Orator's series of 330 operation specimens 5 per cent, and in Newcomb's series 4 per cent. But as Stewart said 'It is clear from the frequency with which well healed sears are encountered in the stomach that the actual proportion of chronic ulcers which become malignant must be much less (d) The proportion of carcinomas which show receptable evidence of having been preceded by ulcers is also small-16 per cent in Stewart's operation series and 13 per cent in Newcomb's (e) The diagnosis of ulcer-cancer should not be made on any single histological criterion, each case must be judged on all the available evidence. Thus Dible in a careful study of 33 early careinomas, found that the hypothesis of their having arisen in ulcers could be rejected immed ately in 19, and could be rejected after thorough microscopical examina tion in a further 9 cases in the 5 remaining cases the findings were compatible with a diagnosis of ulcer cancer but the possibility of an ulcerating sclerosing carcinoma could not be wholly excluded, and in only 2 of these 5 cases was there a long history suggestive of chronic ulceration Hence, in only 2 of 33 cases (6 per cent) did the whole of the evidence sustain a diagnosis of ulcer-cancer

Although I have not made careful studies like those cited above my experience accords with the lowest estimates of the frequency of ulcer-cancer. I have examined many hundreds of gastric ulcers and carcinomas, but have seen only a examples of unequivocal ulcer cancer. During the same period I have seen two instances. Case I and another of the fortuitous coexistence of carcinoma and

simple ulcer separate from each other

Case I—Histori—In 1936 a man aged 51 years had haematemesis, and a diagnosis of gastitic ulcer was made. A high acid curve was recorded. Haematemesis recurred in 1939, when he was again effectively treated for ulcer. Early in 1941 he developed fever, anemal and cough with signs suggesting right basal empyema. Test meal showed complete achieving a Blood examination showed—haemoglobin 25 per cent red corpuscles 13 million white corpuscles 85 000 per cubic millimetre film with many immature cells and many nucleated red cells become a formation of the contained a fungating carennoma at and just below the cardia extending min the costonians. Separated from the growth by 2 centimetres of heality mucosa there was a circular opening in the posterior wall of the stomach near the lesser curvature extending deeply into a mass of fused cancerous costeal lymph glands the appearances storely suggesting penetration of the base of a chronic ulcer into the mass of glands. The surrounding tissues contained pruisels tracks one of which extended along the upper border of the pancreas and into the hitum of the spleen and another opened by a small.

In resected stomachs which of course include very few cancers of the cardia or of the upper part of the lesser curvature or of the whole organ, the proportion of pylonic tumours is greater—in Newcomb's series 57.5 per cent and in Stewart's series 76 per cent.

SPONTANEOUS AND EXPERIMENTAL GASTRIC CARCINOMA IN ANIMALS

Surely it is of great significance that while carcinoma of the stomach is one of the commonest tumours in man it is one of the rarest in all other animals. Wells et al reviewed the few reports of the tumour in mice, rats horses dogs bovines, sheep and fowls. Rudduck and I described an adenocricinoma of the cardia, and Davis and Naylor a diffusely infiltrating pyloric carcinoma, in the dog

The rarriy of spontaneous gastru neoplasms in animals has enhanted the interest of producing these experimentally. The subject, already referred to in Chapter 4, has been dealt with in detail by Pacacok and by Nettleship It must suffice to say here that although it is quite possible that occasional gastric tumours observed in experimental animals after the ingestion of carreino genie substances may indeed have been eaused by these agents the results are too few to warrant final conclusions and much more work in this field is required. Such work is of twofold importance for, if we could discover the conditions necessary for regularly successful production of gastric tumours by known careinogens not only might these conditions be found applicable in human pathology but they might also lead to dependable methods for the biologieal testing of foods and other ingesta for the presence of as yet undertified careinogens. Peacock s and Nettleship s papers show the complexity of the possible causative factors which it may be necessary to reduplicate in order to obtain experimental tumours comparable with human gastric careinom. These will now be discussed

POSSIBLE CAUSATIVE FACTORS IN GASTRIC CARCINOMA

The diets and dietetic habits of civilized man are unnatural on many respects. The substances introduced into the human stomach are endless in their variety quantity and physical state. The problem confronting the research worker in elucidating the causation of gastrie diseases is therefore enormous and complex. He must consider not only the more usual food substances and their possible products under different physical conditions (cooked, smoked tinned frozen etc.) but also a vast number of drugs antiseptics dyes, flavouring agents bacteria and bacterial products which we consume in large amounts. It is not surprising then that many and diverse hypotheses abound but little real know ledge has been gained of the causation of secretory disturbances inflammation ulceration and carcinoma of the stomach and of the interrelationships of these several kinds of lesions. In the following discussion, we will deal first with the pre-cancerous proclinities of the more obvious structural lesions of the stomachulcer, gastritis and benign tumours-and then with the less tangible dietetic and other factors the consideration of many of which is applicable to the ocsophagus also

microscopical study discloses carcinomatous changes in about one quarter of them (as in the specimen of Fig. 178), but also from their association with frank carcinoma Thus, in Stewart's series of 56 stomachs with polypi, cancer was also present in 15 cases (27 per cent), while in 322 cancerous stomachs polypi were

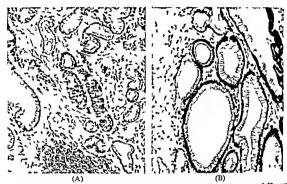


Fig. 178 —Glandular polypus removed surgically from the stomach of a man of 50 years A shows glands with chief and oxyntic cells B shows large goblet-celled glands (× 120)

present in 15 (5 per cent) Spriggs distinguished between multiple polypi and polypoid or hypertrophic gastritis, the latter is inflammatory, often subsides, and is not specially prone to cancerous change. The following case is of interest in that gastric and colonic polypi and cancer of the colon coexisted

Case II -Male aged 78 Necrops) -Stomach contained 5 separate polypoid growths the largest 1 centimetre in diameter Small intestine normal Ascending colon contained 8 separate pedunculated polypi the largest 2 centimetres in diameter and a flat area of Scanding colon contained 8 separate pedunculated polypi the largest 2 centimetres in diameter and a flat area of Scanding Colon Contained Scanding Colon Contained Scanding Colon Contained Scanding Colon Contained Scanding Contained Colon Contained Scanding Colon Contained Scanding Colon Contained Scanding Colon Contained Colon papillary growth 3 centimetres in diameter without metastases Microscopy—Gastric polypi were columnar-celled and gobief-celled papillomas with however several areas suspicious of early malignancy Intestinal polypi were benign but the flat growth was an adenocarcinoma still restricted to the mucosa and submucosa

(b) Adenomyoma" of the stomach

This is a rare lesion described by Stewart and Taylor It appears as a localized but ill defined thickening in the pyloric region which simulates scirrhous carcinoma The thickening is confined however, to the muscle coat and the overlying mucosa Microscopically it shows well differentiated glandular structures of mingled ductular Brunner and pancreatic type with abundant intervening smooth muscle The lesion is a heterotopia rather than a neoplasm and appears to be no more liable to cancerous change than are the heterotopic masses of pancreatic

discharging sinus into the first part of the duodenum. No metastases other than the lymph nodal deposits were found. Microscopy.—Spheroidal-celled carcinoma and adenocarcinoma no growth in the margins of the uleer Comment—Points of interest were the development of achlorhydna during the course of the disease the fortituous coexistence of uleer and cancer and the simulation of a leukaemic blood picture by an extravagant leucocytosis in an anaemic patient.

Such fortuitous coexistence of contiguous ulcer and cancer still further reduces the significance of ulcer as a pre cancerous lesson. Again Mallory pointed out that peptic ulceration in an area of pre invasive carcinoma might lead to appear ances in every way simulating those of 'ulcer cancer. In my opinion then, Stewart's estimate that 16 per cent of cancers arise in ulcers is likely to be an over estimate and Dible's estimate of 6 per cent is likely to be nearer the truth Chronic ulcer must be regarded as only an occasional precursor of cancer, perhaps it does no more than determine the localization of neoplasia in a stomach already prepared for it in a way analogous to the Declman phenomenon in the skin (see Chapter 4)

(2) Gastritis as a precursor of cancer

Konjetzny Orator and Hurst have been the chief proponents of the view that chronic gastritis is a frequent pre cancerous lesion. This view has been opposed by Wanser Hebbel and Guiss and Stewart on the grounds that microscopical evidence of gastritis is very frequent in middle aged and elderly people that the gastritis often seen in cancerous stomachs is non-distinctive and variable in degree and extent that inflammatory changes in cancerous organs must often be secondary to the tumours and that some early carcinomas are unaccompanied by gastritis. However some of konjetzny's beautiful photo graphs depicting attroptie hyperplastic gastritis with prinounied polypoid changes passing into carcinoma certainly support his view and his full and critical discussion of the question cannot be lightly dismissed. He regards ulcer-cancer as only a special example of gastritis cancer the three lesions—gastritis ulcer and cancer—having a close but variable causal telationship to one another. Further thorough studies of stomachs with early carcinomas are needed in order to assess the significance of gastritis as a precursor of neophysia.

(3) Benign epithelial neoplasms and careinoma of the stomach

(a) Papillomas and adenomas

These are only variants of the same group of benign epithelial tumours of the gastric mucosa. They show combinations of solid glandular and appallary structure which includes columnar celled epithelium resembling that of the inner surfaces of the stomach and masses of ga trie or pylone glands (Fig. 178). Their structure distribution and proneness to malignant change have been fully described by Stewart Miller et al and Spriggs. They are situated usually in the body or pre-pylone part of the stomach—they are single in about one half—and multiple in about one half—of the cases, they are more common in men than in women and the mean age of pritients is about 55. Their great tendency to become cancerous is apparent not only from the fact that

Commenting on their findings, Wilkinson (1945) maintained his earlier opinion that the development of gistric caneer, like that of other serious diseases in patients under treatment for pernicious anathma is largely fortuitous. In 1,600 consecutive patients under regular observation he saw cancer develop in only 28, of these, 12 (0.75 per cent) lind cancer of the stomach after periods of from 1 to 17 years, with an average period of 7.7 years, and 9 of the 12 were over 60 years of age when the cancer was diagnosed. Cancer occurred in the large intestine in 5 cases all of whom were elderly. Diabetes developed in 28 cases, and thyroid disease in 36.

In my opinion, the evidence that true pernicious anaemia or achlorhydra predisposes to careinoma of the stomach is inconclusive. The prolongation of the life of pernicious anaemia prutents by modern therapy means inevitably that they will die of other old age discress, of which cancer of the stomach is one of the commonest. It must be remembered too that gastrie carcinoma, with or without metastases in bone marrow, may produce i macrocytic hyperchromic anaemia which has often been mistaken for pernicious anaemia (see p. 409), and that, although this tumour is often fatal within two years, some patients survive for much longer periods as in the following case.

Case III - Histor) - In October 1921 a man aged 65 began to suffer from indigestion vomiting and loss of weight Laparotomy in December showed inoperable gastric carcinoma and the patient was admitted as incurable to the Austin Hospital Melbourne where however he surrived until 1929 his progress being briefly as follows X ray examinations on several occasions showed an enlarging filling defect of the pylone half of the stomach with evidence of pyloric obstruction Fractional test meals on several occasions showed tree hydrochloric acid present usually attaining its peak at 2 hours Progressive hypochromic anaemin appeared with hacmoglobin down to 30 per cent and red corpuscles to 2 million per cubic millimetre Nevertheless he gained weight, and with the passage of time doubt of the diagnosis of cancer was entertained Early in 1928 retention of urine appeared evidently due to prostatic enlargement this became steadily worse and the urine increasingly purulent in spite of bladder wash-outs. The patient died in March 1939 at the age of 73 and 73 years after onset of symptoms of gastric disease Necropsy-Bulky gelatinous adenocartinoma of pylone half of stomach with nodular infiltration of the lesser omentum but no metastases Cause of death-prostate enlargement, suppurative pyclonephritis

Cases of gastric cancer of long duration, like the foregoing, show that an interval of several years between the appearance of anaemia and the discovery of a gastric neoplasm cannot be taken as conclusive proof that the former preceded the latter. The only cases in which it can be claimed with certainty that the anaemia preceded the tumour are those in which typical blood changes, including leucopenia, and a typical response to liver therapy were observed several years prior to the appearance of the tumour, and in which expert radiographic examination of the stomach initially showed no abnormality. Some of the cases reported fulfil these criteria, but are they so numerous that they cannot be accounted for by the fortuitous development of a tumour which is very common in elderly people? This is still arguable and further carefully evaluated data are necessary before final decision can be reached.

(5) Possible carcinogenic substances ingested

The needle in the-haystack simile is particularly appropriate to the search

tissue found in the stomach intestine or Meckel's diverticulum. Nicholson described and referred to cases of carcinoma of heterotopic pancreatic tissue.

(4) Pernicious anaemia and achierhydria as precursors of cancer

In 1929 Hurst advanced the view that the achlorhydria frequently accompanying gastric carcinoma was not the result of the timour but had preceded it. He eited cases in which achlorhydria had been known to be present in patients who later developed gastric cancer, and others in whom pernicious anaemia preceded cancer, and he supposed the achlorhydria to result from previous chronic gastritis. He also described cases of ulcer cancer in which the acidity was undiminished by the onset of the cancer and concluded that when free acid is present it is generally secondary to gastritis. However that the achlorhydria which often accompanies gastric carcinoma does not always precede the timour is shown by Case I above, and by that cited by Stewart in which hyperchlorhydria was known to have been present 21 years prior to laparotomy by which time achlorhydria had developed and necropsy showed an ulcer cancer. I know also of other cases in which a achlorhydra developed during the course of carcinoma of the stomach.

Relevant here are observations on the gastrie secretions of groups of people differing in their hability to gastrie cancer Lintoit found no significant difference between the test meal analyses of English and Dutch people or between those of the upper and poorer classes. Although the Chinese and Malays in Java differmarkedly in the incidence of both ulcer and cancer of the stomach, Bonne et al found no differences between the two races as regards either gastrie secretion of

the structure of the gastrie mucosa

In 1933 Wilkinson gave a detailed account of the diseases he had observed to develop in 370 cases of pernicious anaemia. These included 8 cases of careinoma the sites of which were the buccal cavity in 3 cases, stomach in 2 uterus in 2 and colon in 1 case. He regarded the association of pernicious anaemia and malignant disease as fartely fortuitous.

In 1938 Washburn and Rozendaal reported that in 906 consecutive cases of perincious anacmina gross gastine lessons had been found in 24 comprising carcinoma in 16 and polypi in 8 and from the literature they collected references to 75 cases of coexisting pernicious anaemia and gastric carcinoma. They gave details of 7 of their patients in whom the anaemia had long antedated the development of carcinoma. Spriggs also commented on the frequently reported associal

tion of gastric polypi with perniesous annemia

In 1945 Kaplan and Rigler reviewed the subject afresh and reported 293 more concepts on cases of permicious anaemia of which 36 had carcinoma of the stomach a proportion three the expected Kaplan and Rigler therefore concluded that there is a definite causative relationship between permicious anaemia and gastine cancer and recommended that patients with permicious anaemia and be submitted to regular clinical and X-ray examination to detect early new growths of the stomach Rigler et al. by earlying out this suggestion on 211 patients claimed to detect carenoma in 8 per cent and polypi in 7 per cent. The diagnosis of permicious anaemia in Kaplan and Rigler's series however, is questionable for some of their cases perhaps some cases of carcinoma with a permicious like anaemia were included.

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(5) Possible careinogenic substances ingested

The needle in the haystack simile is particularly appropriate to the search

for possible carcinogens in human ingesta. There are two principal methods of attacking the problem-(a) clinical inquiries like those of Craver. Herbert and Bruske, into the diets (including alcohol drugs etc.) of patients with gastric or oesophageal cancer or of communities particularly prone to these tumours with adequate control series for comparison and (b) experimental inquiry aiming at the production of gastric tumours by factors comparable with those operating in man as discussed by Peacock, Nettleship and Kirby Although a beginning has been made along both of these lines of inquiry little of positive value has yet emerged. A great field awaits exploration, and so diverse and complex are the problems that significant results will be attained only by extensive. carefully designed and well informed research. Some of the possible factors involved deserve brief mention

(a) Alcohol

Alcohol has often been suggested as a possible cause of oesophageal and eastric as well as of buccal and pharyngeal tumours. Some evidence for this suggestion is afforded by (a) the high mortality rates from oesophageal and castric cancer recorded for dock labourers furnacemen stevedores barmen and some other occupational groups supposed to be specially addicted to alcoholic drinks and the low mortality rates from these tumours recorded for dentists doctors civil servants teachers professional engineers draughtsmen barristers typists and clerks (Registrar General's Decennial Supplement 1938) aleoholie habits recorded of patients with oesophagual cancer by Craver and others and (c) the heavy consumption of alcohol, especially as strong spirits. by the Dutch and some other peoples with a high incidence of gastric cancer All of this evidence however is no more than strongly suggestive many factors other than alcohol may be concerned in the differences in question. Supposing that alcoholic drinks are indeed a real factor in the causation of occombaneal and gastric cancer it may yet be that the alcohol itself is less to blame than other ingredients of various spirits wines and liqueurs or that the concentration of the alcohol is an important factor Perhaps Daniel Quilp who drank Schiedam strong and fiery as raw spirit and could swallow half a pint of boiling rum

neat avoided cancer of his stomach only by drowning !

(b) Careinogenie hydrocarbons

These must be considered as possible ingredients of foods Kennaway s finding that many kinds of organic substances heated to charring temperatures yielded careinogenic artificial tars is surely not without culmary significance Roasting grilling frying and toasting may well produce in small quantities the same careinogens as were present in Kennaway's artificial tars and the life long ingestion of these may be a major cause of our common alimentary cancers. Fats used repeatedly for frying would seem to be the most likely material in which to commence the search for possible carcinogens and Peacock Kirby and Beck (cited in Chapter 4) have already published promising preliminary work of this kind Smoked fish also should certainly be investigated. Other possible sources of ingested carcinogenic hydrocarbons include tobacco tar, dust from tarred roads and domestic and occupational soots and smokes

(c) Other chemical carcinogens

These may exist amongst the great variety of drugs, flavouring agents colouring agents and preservatives which man eonsumes

Biological testing of all suspect substances will be necessary to detect the offenders

The supposition that ingested non absorbable, or only slightly absorbable, chemical carcinogens may be largely to blame for alimentary malignancies has much to commend it on theoretical grounds. Admitted to the stomach such substances would often remain in contact with its mucous membrane for several hours at a time. In the small intestine, however, they would be considerably diluted and hurried through the bowel quickly. In the large intestine they would again be concentrated and would lie in contact with the mucosa for long periods. This would accord with the relative frequency of cancer of the stomach, large intestine and small intestine. It would also accord with the rarity of all alimentary cancers in animals, whose food is seldom fried, roasted or smoked, and who do not consume large amounts of drugs, dyes, flavouring and preserving agents of tobacco.

(6) The physical state of ingested food

(a) Temperature

The temperatures at which fluids can be imbibed with comfort are surprisingly high. Personal experiments show that fluids at 50°C (p. e. the temperature of a 'scalding hot' bath) are 'luke warm'' to drink, at 65°C (paistering temperature) comfortably hot'' to drink, and that at 75°C (blistering temperature for the skin) fluids feel 'very hot'' but can be swillowed without apparent injury. A piece of unmasticated food such as a lump of potato or meat, can be swallowed while its internal temperature is only a few degrees below boiling point. Clearly then the oesophagus and stomach are constantly being subjected unwittingly to thermal insults of a degree which our skins would not tolerate. Whether such insults may be directly or indirectly carcinogenic remains to be proved. Craver's inquiries suggested that food temperatures may have played some part in the causation of gastric cancers but not in that of oesophageal cancers. Herbert and Bruske found that the Dutch take their food hotter than the English.

(b) Imperfect mastication

Imperfect mastication, resulting either from habitual haste or from dental disease or lack of teeth, no doubt occasions repeated minor injuries of the oeso phagus or stomach. It is indeed surprising what people will swallow whole. I have found impacted against a stenosing carcinoma of the colon a collection of cherry stones along with the initiat bones of most of the limbs and trunk of a rabbit. Craver found poor teeth or lack of teeth to be the most prominent item revealed by his inquiry in cases of gastric cancer, and one of the most prominent in oeso phageal cancer. Yet as far as I know, there is no evidence that hair eaters or lunatics who swallow foreign bodies are predisposed to cancer of the oesophagus or stomath. Moreover cattle, goats sheep and other herbivores often ingest and retain many kinds of foreign bodies vet gastric tumours are as infrequent in them as in other anim is

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Bowen's disease of the epiderms and clearly shows simultaneous or successive cancerous change over a wide field of mucous membrane. The very diffuse forms of gastrie carcinoma such as "gizzard" or "leather bottle" stomach owe their wide extent not solely to their infiltrative growth but also to their widespread.

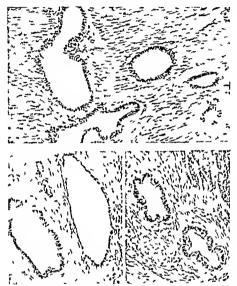


Fig. 179—Three parts of highly differentiated adenocarcinoma infiltrating pastric muscle, from a diffusely infiltrating growth in a man of 52 years. (× 120)

origin Discussion as to whether earemomas arise mainly from glands or from the surface epithelium is pointless, it is clear from the study of early non invasive growths that the whole of the epithelium in the affected area participates

THE STRUCTURE OF GASTRIC CARCINOMA

(1) Macroscopic forms of growth

For descriptive purposes the following forms may be distinguished

(1) Polypoid or fungoid carcinomas of predominantly endogastric growth

(2) Ulcerated plateau like carcinomas, with prominently elevated rampari like nodular borders

(7) Heredity and gastric cancer

Inherited predisposition to gastrie careinoma, revealed by occasional cancer families or by the slightly enhanced expectation of this disease appearing amongst the immediate relatives of sufferers from it (see Chapter 5) is certainly not a very important factor in causation. Of historical interest is the predisposition of the Bonaparte family to gastric carcinoma Although doubt of the diagnosis of cancer in Napoleon's case has been expressed in my opinion Antommarchi's full descrip tion of the post mortem findings (cited by Chaplin) makes it clear that the disease was indeed an extensive carcinoma of the lesser curvature and adjacent walls spreading to the surrounding peritoneum and lymph glands The little epiploon was contracted swollen, extremely hard and degenerated The lymphatic glands of this peritoneal covering those which are placed along the curves of the stomach and those which are around the pillars of the disphragm were in part tumefied and scirrhous and some even in a state of suppuration Sokoloff collected the medical histories of Napoleon's relatives. His father died at the age of 39 with cancer of the stomach proved by necropsy his youngest sister Caroline also died of gastric cancer two other sisters Elisa and Pauline died at ages of 43 and 44 years of gastric disease from their historics almost certainly carcinoma and one of his brothers. Lucien died at 65 probably of earcinoma of the stomach

THE MODE OF ORIGIN OF GASTRIC CARCINOMA

Hauser Verse Konjetzny and others have all described specimens which show many that gastric carcinoma may arise in a widespread or multicentric manner from more or less extensive areas of mucous membrane. According to Konjitzny multicentric development of gastric carcinoma is the rule. In opinion which is convincingly supported by his many excellent illustrations. He gives references also to recorded cases of grossly multiple carcinomas to which may be added Tsunoda's case of three separate areas of cancer in a stomach, and the following two cases.

Case IV—Male aged 64 Necrops—Stomach showed (i) stregular ill-defined area of flat growth 7 centimeters in diameter on animetor wall near cardia involving all coats and producing plaque like thickening of serous coat (ii) a similar ill-defined region of thickening on the greater curvature near the pylorus (iii) intercning gastric wall healthy Pengastric and lumbar lymph gland were enlarged by growth but there were no other metastases. Microscopy—Deffucely infiltrating spheroidal-cell carcinoma in both areas of stomach with more cellular deposits in lymph glands.

Care I — Female aged 64 Accrops) — Stomach showed (i) a projecting fungood growth is centimetre in diameter attached by an infiltrated pedicle 3 centimetres in diameter to the greater curvature 3 centimetres proumal to the pylorus and with several enlarged cancerous lymph glands in the adjacent omental attachment (ii) an irregular growth involving most of the circumference of the cardia with no accompanying lymph nodal deposits (iii) intenening stomach wall healthy. Lore contained a few scattered metastases all other organs clear. Microscopy—Both gastine tumours and the hepatic metastases showed disorderly adenocarranoma.

Schneider described two separate histologically different carcinomas in one stomach and referred to 9 similar reports. Cancerous change in a polypus is often demonstrably widespread or progressive. Non polypoid pre invasive carcinoma or carcinoma in situ as described by Malloty is analogous to

variants are seen

- (a) Adenocarcinoma or adeno populary carcinoma showing distinct differ entiation of acinar structures of varying degrees of perfection (Figs 32 and 179)
- (b) Mucord adenocarcinoma, a viriant of (a) in which mucus secretion is prominent, often producing large amounts of extra cellular gelatinous mucus in parts of which only scanty isolated groups of tumour cells are present

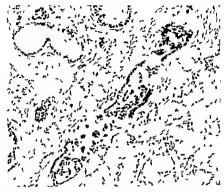


Fig. 181 -- Pyloric carcinoma invading duodenum amidst Brunner's glands (× 120)

- (c) Signet ring cell carcinoma, consisting mainly of spherical mucus containing cells with their nuclei thrust to one side (Figs 44 50, 180, 182 and 183)
- (d) Infiltrating spheroidal-cell carcinoma, identical with (c) except that the cells show little or no secretion, secreting and non secreting spheroidal cells are often seen together especially in the diffuse forms of growth
- (e) Metaplastic squamous cell carcinoma is rare in the stomach, usually in parts only of a tumour of mainly adenocarcinomatous structure
- (f) Highly cellular anaplastic carcinoma is frequent, forming soft, necrotic or haemorrhagic growths consisting of disorderly masses of rapidly multiplying poorly differentiated cells with little or no glandular orientation. Some haemorrhagic tumours of this kind have had a misleading chorion-epithelioma like appearance, especially in their metastases in the liver (Risel. Stewart 1913). Gaeriner)

It must be emphasized that the names (a) to (f) do not denote entities but only structural variants of the entity gastric carcinoma, and that several or all of them may be seen in a single tumour I agree with Stout that 'it is not only a

- (3) Ulcer like carcinomas without prominent ramparts or well defined borders but with diffuse infiltration of the neighbouring stomach walls
- (4) Extensive diffuse carcinomas producing more or less uniform thickening of part or whole of the stomach walls with only slight superficial ulceration or none at all

These gross forms are of course, not sharply distinct tumours showing various combinations of them are common Microscopically group (1) shows mainly adeno papillary structure group (4) mainly infitrating spheroidal celled or signet ring celled structure while groups (2) and (3) show all possible structural

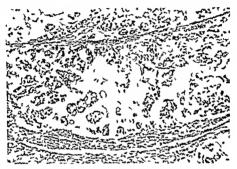


Fig. 180 -Signet ring-cell mucoid carcinoma of stomach (× 72)

variants. Mucus secretion may be visible to the naked eye in any of the forms of growth, but is most conspicuous in group (2) producing massive irregular gelatinous tumours. The commonest situation of diffuse carcinomas, when these are restricted to part only of the wall of the stomach is the pyloric part whence they spread more or less extensively towards the cardin. When they affect most or the whole of the organ they produce the gizzard or leather bottle stomach often with great contraction and rigidity of the organ. In spite of the great thuckening of the wall often up to 2 centimetres or more the various coats especially the muscular layers often remain clearly distinguishable on the cut surface. Indeed, in many cases the prominently thickened muscle layers appear to have undergone hypertrophy.

(2) Microscopie structure

All careinomas of the stomach are of course glandular in origin but the extent to which glandular differentiation appears in them vaties widely from tumour to tumour and also in different parts of one tumour. The following structural

tubules a carcinoma shall form before it is to be called adenocarcinoma? How much must be secreted in order that a tumor shall be called a colloid or mucoid carcinoma?" I also agree with him that attempts to predict the degree of malignancy, the rate of growth and the probable success or failure of surgical treatment bised on cellular differentiation alone are of very little value when applied to an individual case, although some small percentage of difference may appear in large groups

THE DIRECT SPREAD OF GASTRIC CARCINOMA

Besides diffuse spread in the walls of the stomach itself, gastric cancers extend also into the walls of the duodenum and oesophagus and into the gastrohepatic and gastrocolic omenta, the pancreas, spleen, transverse colon, liver and dia phraem

The prevalent view that careinoma of the stomach seldom extends into the diodenium is talse microscopical examination of resected stomachs as well as those obtained at necropsy will often disclose infiltration of the diodenal submucous or muscle coats for distances of 2 centimetres or more beyond the pilorus (examples and references by Castleman, and Figs 34 and 181). This is of practical importance, it means that all gastrectomies for pyloric carcinomas should include if possible a diodenal cuff of 3 centimetres, and that this should be examined microscopically for extensions of the growth

Some carcinomas of the cardia region spread grossly into the lower part of the *oesophagus*, and may simulate primary oesophageal growths. In other cases, extensions of growth take place through the lymphatics or veins of the submucous and muscle coats and lead to areas of ulceration in the oesophagus.

which appear to be separate from the main growth in the stomach

Direct extension of gistric carcinomas to the investing peritoneum and to the greater and lesser omenta is of course very common and is the usual source of trans peritoneal dissemination. Many pyloric growths also invide the pancreas directly and invasion of the bile duct or of the portal tem or its main tributaries is not unusual. Through the gastrocolic omentum the transferse colon may be invaded and gastrocolic fistula may develop. Direct invasion of contiguous parts of the liner occurs frequently. Perforation of gastric cancers into the peritoneal cavity, an accident much less common than with chrenic ulcers has been well described by Aird.

Invision of the spleen may take place either directly from the primary growth or from deposits in the splenic lymph glands. The growth usually enters the spleen at its hitim and spreads mainly along its trabeculae, and the trabecular extensions may reach even to the capsule of the convex surface of the organ. The main trabecular veins often suffer invasion. I have seen four cases in which sloughing splenic tissue formed part of the floor of ulcerating cancers of the stomach and serious—in two cases fatal—haemorrhage had taken place from the necrotic spleen.

Limphatic permeation is often plainly visible in the neighbourhood of gastric carcinomas, appearing as finely nodular white lines on the peritoneal surface of the storach itself or in the omenta adjacent to it. Microscopical study recals that from some of the diffusely infiltrating growths very widespread permeation.

waste of time but also deceptive to attach histologically descriptive adjectives and prefives to gastric carcinomas. Who is to determine what proportion of

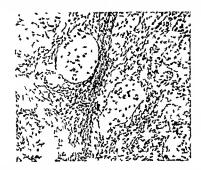


Fig. 182—From a Arukenberg tumout of the ovary in a woman of 59 years, showing signet ring-cells within lymphatics. Ovarian stroma and part of a corpus albicans also are visible (x 120).

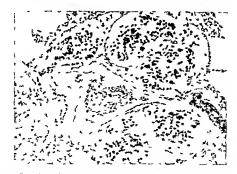


Fig. 183 —From lung of same case as Fig. 182 showing perivascular lymphatics distended by signer ring-cells and mucus. (x 120)

(3) Transperitoneal metastasis

Peritoneal dissemination from gastric careinoma is very frequent, it had occurred in 26 of my 85 necropsy cases (31 per cent), and in 61 of Stout's 143 cases (43 per cent). It produces scattered discrete nodules, extensive plaque like infiltrations or massive gelatinous collections with or without ascites. Hernal sacs sometimes share in the peritonical dissemination, and deposits in the recto vesical or recto uterine pouch may simulate primary careinoma of the rectum (Konjetzny pp 1812, and references in Chapter 10). Secondary growths in or near the umbilicus may be due to spread from peritonical deposits on the round ligament of the liver.

Ovarian metastases

These occur more trequently from gastric carcinoma than from any other tumour and in most cases they arise by the trans peritoneal route accounts and many examples see Glockner, Stone Gauthier Villars Willis (1934, Chapter XXIII), and Konjetzny (1938, pp. 1846). Gastric cancer was responsible for 75 of the 133 cases of secondary growths in the ovaries reviewed by Stone, for 247 of the 365 cases of alimentary cancer with ovarian metastases reviewed by Gauthier Villars, and for 6 of my 16 necropsy cases with secondary carcinoma in the ovaries (1941) Thus, at least one third, possibly one half, of all secondary growths in the ovaries are from carcinoma of the stomach. The proportion of cases of gastric carcinoma with ovarian metastases has varied in different series from 3 per cent (Poscharissky) to 14 per cent (Stout), but these series included cases of both seves and the incidence of ovarian metastases in females only is more than double these figures, e.g. in Poscharissky's series 16 of 155 cases (10 per cent) My 6 cases with ovarian metastases occurred in a consecutive series of 28 necropsies on women with gastric cancer, a frequency of 21 per cent. The mean age of patients with secondary growths in the ovaries is decidedly less than the mean age of the subjects of gastric cancer in general, the former being between 35 and 40 and the latter in the sixth decade (Willis, p 306 Konjetzny p 184) clearly the functionally active ovary is more prone to metastasis than is the senile ovary

The gross and microscopical structures of the ovarian metastases of gastric carcinoma vary greatly. Some are acinar adenocarcinomas with or without cystic or pripilary characters. Many others however show in whole or part the distinctive structure of the Krukenberg tumour. In 1896 Krukenberg described as fibrosarcoma mucocellulare carcinomatodes" a diffusely infiltrating often bilateral solid tumour of the ovaries of myxomatous appearance, consisting of mucus containing signet ring cells scattered amidst abundant oedematous ovarian stroma. Krukenberg beheved these tumours to be ovarian in origin but later study showed that most probably all of them are metastatic growths and that carcinoma of the stomach is by far their commonest source (Major Shaw and other references by Willis 1934, pp 310 312). The term Krukenberg tumour should be reserved for growths showing the characteristic structure (Fig. 182) and should not be applied—as his often been done—to other kinds of secondary carcinoma in the ovaries. On the other hand Krukenberg tumours are not sharply distinct from other metastatic growths for tumours of combined

of lymphatics has taken place in all the surrounding tissues, and occasionally almost body wide lymph vessel carcinosis is present (Schierge Schmucker Dawson) In such cases however, permeation has not proceeded solely from the primary growth but also from many metastatic foci established by embolism in lymph glands or lymphatic plexises (see Chapter 9)

THE METASTASIS OF GASTRIC CARCINOMA

(1) Metastasis to the regional lymph glands

Even in operation specimens the perigastric lymph glands are found to contain tumout in the majority of cases, the proportions lying between 50 and 70 per cent in most series. In necropsy cases the percentage is of course higher, e.g. in 76 of 85 cases which I reported in 1941 (89 per cent) in an identical proportion of 850 to 1 s 143 cases, and in 68 per cent of Poschartssky's 500 cases. The presence or absence of lymph nodal metastases can be determined only by careful dissection and microscopical examination—and most estimates of the frequency of metas tases are under estimates (Fig. 44)—Lymphatic micrastasis is the main factor affecting the prognosis of resectable tumours—e.g. Walters et al. found that of 919 operation cases without deposits in the glands 43 per cent survived 5 years or longer but of 1049 cases with affected glands only 16 per cent survived for 5 years. Most of the few 5 year survivors may be regarded as permanently cured—but Pain reported a case of recurrence 12 years after partial gastrectomy—whether from residual growth or from fresh cancerous change in the remainder of the organ is uncertain.

(2) Further metastasis by lymphatic channels

From the perigastric lymph glands the tumours often spread quickly and widely to the coeliac lumbar, mesenteric pelvic and mediastinal glands. From the coeliac upper lumbar and mesenteric glands invasion of the cisterna ehylic or its main tributaries often occurs and gastric carcinoma is responsible for about one third of the cases of cancerous disease of the thoracic duct (Willis 1934, Chapter III). About 10 per cent of necropsy cases of cancer of the stomach show massion of the cisterna chylic of 7 of 85 cases (Willis, 1941). Affection of the thoracic duct or its main tributaries often results in embolic dissemination to the lungs and thus partly accounts for the fact that gastric cancer is the tumour most often responsible for military carcinosis of the lungs.

Troisier's sign , enlargement of the supraclavicular lymph glands usually of the left side in cases of abdominal malignant disease (Troisier 1889) is most often due to carenoma of the stomach and in most cases is associated with involvement of the thoracie duct. Its frequency is estimated variously as between 3 and 15 per cent of fatal cases e.g. in 5.4 per cent of Poscharissky's series and in 13 of my 85 cases (15 per cent).

Gastric carcinom: is one of the most frequent sources of secondary growths in the abdominal walls especially in or near the umbilicus. In most cases these are due to lymphatic dissemination along the round ligament but in some cases they arise by direct spread from the primary growth or from peritonical metastases (See Quénu and Longuet. 1896. Willis. 1934, pp. 386-7., and Konjetzny, 1938, p. 183).

endocarditis malignant malaria and primary aplastic anaemia. Haemoglobin was reduced to 20 per cent and red corpuscles to less than one million while white corpuscles numbered 15 000 per cubic milliametre. Death occurred in October about 3 months from the onset of symptoms. Necropsy showed a soft ulcerated caremona 3 centimetres in diameter on the posterior wall of the pyloric antirum with soft haemorrhagic deposits in many abdominal and mediastinal lymph glands and extensive ill defined areas of metastitic growth in many hones. No other organs contained obvious growths but there were widespread petechial and larger haemorrhages in many tissues. Microscopy—Different parts of the tumours in the stomach lymph glands and bones showed mucoid adenocarcinomas spheroidal and signer ring cell carenoma and anaplastic relialar growth. The small blood vessels and lymphatics of the lungs showed widespread tumour infiltration accompanied by haemorrhage.

(d) Other metastases

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No organ or ussue is exempt from blood borne metastases from gastric carcinoma. They are not uncommon in the adrenals kidneys and myocardium they are unusual in the thyroid brain meninges and skin and are rare in other issues (Willis 1934). Senge saw metastases in the placenta. The secondary growths in the breasts described by Stahr and by Dawson probably arrived by way of lymphatic paths, and the same may apply to some deposits in the meninges as in the cases of Knierim and Cornwall. In other cases however, meningeal dissemination is secondary to a metastasis in the brain as in Duncan a case.

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adenocarcinomatous and signet ring-cell structure are seen. The kind of gastric growth usually responsible for Krukenberg tumours is the diffusely infiltrating spheroidal cell or signet ring cell carcinoma. The primary growth is often small and relatively symptomless, the large ovarian tumours giving the first or main signs of disease. Skiagrams of the stomach may fail to disclose any abnormality, and even at necropsy a small diffuse primary growth may escape detection. Hence the necessity for adopting very strict criteria before accepting supposed cases of 'primary' 'krukenberg tumours of the ovary. Apart from secondary deposits in the perigastric lymph glands and sometimes in the peritoneum. Krukenberg tumours are often unaccompanied by metastases in other organs.

(4) Metastasis by the blood stream

(a) The liver

The liver contains discrete metastases in a high proportion (at least one third) of fatal cases e.g. in 33 per cent of haufmann s. Basle cases, in 36 per cent of Poscharissky's and in 46 per cent of my 85 cases. These clearly arise by embolism following, invasion of main tributaries of the portal vein (Willis. 1930)

(b) The lungs

The lungs show secondary growths in about one quarter of fatal cases e.g. in 19 of my 85 cases. In 14 of these 19 cases the pulmonary growths were discrete and clearly blood borne in the other 5 cases there was widespread permeation of peribronchial and subpleural lymph vessels with some nodulation (Fig. 183) and it was uncertain whether the growths had reached the lungs by the bloodstream or by retrograde lymphatic spread from affected hiar lymph glands. In 4 additional cases tumour emboh were found microscopically in the arterioles of lungs which showed no visible growths to the naked eye. The difficulty just mentioned of distinguishing between haemic metasiasis followed by lymphatic permeation in the lungs and nodular lymphatic spread from hihr deposits, must arise in many cases of miliary carcinosis of the lungs secondary to gastric cancer a condition with which pathologists have long been familiar and which is now well recognized by radiologists also as sometimes producing skiagrams as well as naked eye appearances, suggesting miliary tuberculosis (Funk and Crawford Gloor Achard et al.)

(c) Bones

Bones contain metastases in between 5 and 10 per cent of fatal cases. Occasion ally, these produce serious local results such as tumour or pathological fracture, which may simulate primary skeletial disease as in cases described by Konjetzny and myself (1938). In an important group of cases, widespread metastases in bone marrow often from small relatively symptomiless primary growths seriously affect haemopoiesis and produce severe megalocytic anacmia or thrombocytopenia (Harrington and Teacher, Harrington and Kennedy. Seeman and Krasnopolski Laurence and Mahoney other references by Willis. 1934. pp. 324. and 342-4, and the following case).

Cate I I - History—In July 1943 a man aged 36 who had been on active service in the tropics began to suffer from weakness pyreus and pallor. These symptoms became repully worse and diagnoses made during ensuing weeks included acute bacterial

CHAPTER 22

EPITHELIAL TUMOURS OF THE SMALL INTESTINE

EPITHELIAL tumours of the small intestine are much less common than those of the stomach or large intestine. My necropsics include 17 cases of carcinoma of the small intestine, as against 227 of the stomach and 190 of the large intestine. These were briefly as follow.

SUMMARY OF 17 NECROPSY CASES OF CARCINOMA OF THE SMALL INTESTINE

| Case No | Sex age | No and sites of tumours | Histology | Metastases |
|-------------------------------|--|--|--|---|
| I II IV V VII VIII IX X | M 66 M 77 M 37 M 67 M 56 M 41 M 68 F 70 M 25 M 44 | 3 ileum Many throughout Single ileum Sungle ileum Many throughout Many jejunum 7 ileum Many ileum Single upper jejunum Single duodenum | Argentaffin carcinoma Argentaffin carcinoma Argentaffin carcinoma Argentaffin carcinoma Argentaffin carcinoma Argentaffin carcinoma Argentaffin carcinoma Argentaffin carcinoma Anaplastic carcinoma Adenocarcinoma | None None None Lymph glands liver Lymph glands kidney In many organs Brain and other parts None Lymph glands Lymph glands thoracic |
| хı | F, 70 | Single upper jejunum | Adenocarcinoma | duct lungs Lymph glands liver, peri |
| XII XIV XV XV XVI | F 72 M 62 M 71 F 50 F 53 | Single duodenum Single upper jejunum Single duodenum Single duodenum 2 duodenum and upper jejunum Single upper jejunum | Adenocarcinoma Adenocarcinoma Adenocarcinoma Adenocarcinoma Anaplastic carcinoma Adenocarcinoma | None Lymph glands Lymph glands Lymph glands liver lungs Lymph glands liver lungs adrenal Lymph glands thoracie duct lungs liver ovary |

Nos I to VI and IX to XII have been described elsewhere (Willis, 1940 and 1941)

- I shall describe enteric epithelial tumours under the following heads
 - (1) Benign tumours of the small intestine
 - (2) Non argentaffin carcinomas of the small intestine
 - (3) Argentaffin carcinomas of the small intestine
 (4) Tumours of yitello intestinal structures
 - (a) of Meckel s diverticulum
 - (b) of the umbilious

BENIGN TUMOURS OF THE SMALL INTESTINE

These are very rare In my necropsy work I have not encountered any papillary or adenomatous polypi comparable with those of the stomach or large intestine

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relationship is very doubtful. Reports of enteric careinoma coexisting with tuberculous enteritis, syphilis or other infections are too few to be significant

(5) Metastases

These are found in the neighbouring lymph glands or in the liver in more than on-half of fatal cases but metastases in lungs and other organs are infrequent My Case X showed invasion of the thoracic duct with resulting profuse embolic dissemination to the lungs (Fig. 47), and in Case XVII the thoracic duct was occupied by tumour right up to its cervical exit from which a polypoid mass of growth projected into the great veins, and there were multiple metastases in the lungs, as well as in the liver and right ovary

ARGENTAFFIN CARCINOMAS OF THE SMALL INTESTINE

These tumours are still insufficiently known to pathologists and surgeons. They occur nearly as frequently as the adenocaremomas just described, e.g. in

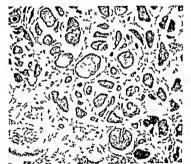


Fig. 184 -- Typical structure of argentaffin carcinoma (× 55)

8 of my 17 necropsy cases of enteric careinoma and in 30 of 130 cases of tumours of the small bowel in Dockerty and Ashburn's series. For other good accounts of these growths see Cope and Newcomb, Cooke, Marangos, Humphreys, Ariel Willis (1940) and Dangemond.

(1) Nomenclature and histogenesis

The frequently used name carcinoid tumour', introduced by Oberndorfer in 1907, is an unfortunate one, implying a reputation of innocence which later experience has shown to be undescried. Many "carcinoids", of the small intestine especially are dangerously invasive and metastaxizing growths. They should be called argentaffin or Kultschitzky cell carcinomas, since there is clear

Baggenstoss refers to some reported cases, and records 25 examples of small polypi 2 to 5 millimetres in diameter situated on the duodenal papilla. Feyrter describes several specimens of nodular hyperplasia or circumscribed adenoma of Brunner's glands.

NON ARGENTAFFIN CARCINOMAS OF THE SMALL INTESTINE

Adenocarcinomas of ordinary structure and of varying degree of differentiation are the commonest tumours of the small intestine. These appear as annular stenosing ulcerated or polypoid growths and usually cause intestinal obstruction

(1) Site

The most frequent sites are the second part of the duodenum and the upper part of the jejunum Hoffman and Pack recorded that of 228 carcinomas of the small intestine 104 arose in the duodenum Duodenal carcinoma has been well described by Meyer and Rosenberg Rutishauser, Hoffman and Pack, Stewart and Lieber Lieber et al and Baggenstoss. It arises most frequently in or near the papilla of Vater and it is often difficult to decide whether the tumour is ampullary or duodenal in origin. In advanced cases it is often impossible also to distinguish a duodenal from a pancreatic carcinoma. Beyond the duodenum the favourite site of enteric carcinoma is in the first two feet of the jejunum where the growth is usually of tightly stenosing annular form. Of 6 surgically resected specimens which I have examined 4 were from the upper part of the jejunum Adenocarcinomas of the ileum are rare, those of the flee caseal orifice are more often caseal than iteal.

(2) Age incidence

This is similar to that of gastro intestmal carcinoma in general. The mean age of the combined series of patients with duodenal carcinoma cited above was 55 years and that of my 9 necropsy cases 57 years. The lowest age recorded is 16 years.

(3) Sex meidence

Men are affected more than women especially from duodenal careinoma the sex ratio being about 2 to 1 in most series Of my 7 upper jejunal careinomas—3 necropsy and 4 surgical specimens—5 were from women

(4) Antecedent lesions

These have rarely been seen. Meyer and Rosenberg and konjetzny (1938 p 120) have referred to cases of duodenal cancer supposed to have supervened on chronic uleer—but these are exceptional some of them are dubious, and in some others coexistence of the two lesions may have been fortuitous. It is notable that duodenal carcinoma develops much more frequently in the periampullary region than in the first part of the organ where most uleers occur. Stewart and Lieber found no evidence of previous chronic uleer in their 6 cases of supra papillary carinoma. Gall stones are recorded in a small proportion of cases of periampullary, cancer. c.g. in 5 of 28 cases (Baggentioss), but a causative

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necropsy cases 2 showed solitary tumours, one showed 3 tumours and 5 showed many tumours. Cooke found them recorded as multiple in 27 of 76 cases, but these included surgically removed as well as necropsy specimens Visible multiple growths often number 20, 40 60 or more, but in addition to the visible ones the mucosa often contains many tiny tumour foci which are disclosed only by microscopical search. The ileum is usually more affected than the jeiunum. but in my Case VI there were visibly multiple tumours in the jejunum only Multiple enteric growths may be accompanied by tumours in the stomach or pancreas. and it may prove difficult to decide whether these are metastases or truly multiple growths (Willis, 1940)

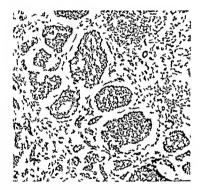


Fig. 186 —Typical structure of arcentaifin carcinoma in a metastasis in the liver (× 90)

Young tumours usually take the form of nodules or plaques projecting into the bowel lumen and covered by intact mucosa. As they enlarge they often show central umbilication or ulceration Older growths, especially solitary ones may encircle the bowel and eause infolding of the muscle coat and stenosis, well depicted by Humphreys Microscopical study reveals that even small seemingly well defined tumours have often sent fine extensions into the muscular and serous coats (Fig. 185), as this infiltration extends, it may cause dense fibrosis of the tissues, and may be accompanied also by apparent hyperplasia of the invaded muscular tissues The yellow colour of the tumours is retained in all these situations, and often in metastases also

(3) Age and sex incidence

The tumours are found chiefly during middle or old age the mean age of my 8 necropsy cases was 60 years, of Dockerty and Ashburn's 13 cases with metastases evidence that they arise from the specialized granular epithelial cells of the crypts of Lieberkuhn, the yellow cells of Kultschitzky later shown by Masson to have selective argentaffin staming properties. The funtour cells show silver staniable granules like those of the Kultschitzky cells, and the cut surface of the tumours, like the cells from which they arise, often show a characteristic yellow or orange, colour. In most cases these caremomas are histologically so distinctive that they can be identified readily without using the somewhat fickle silver staming test (Tygs 184 186). They typically consist of well defined solid clumps or strands of rather small closely packed polyhedral cells with here and there small glandular

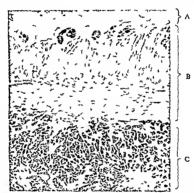


Fig. 185 — Microscopic degree of infiltration by argentaffin carcinoma to outer coats of bowel A = scrosa B = muscularis $C = main mass of growth in submucosa (<math>\times$ 32)

lumina or distinct acini. The more actively growing tumours show varying degrees of anaplasia in part or whole (Figs. 187, 188), so that they may escape immediate histological recognition (as in Case V, Willis 1940).

The causation of argentaffin carcinomas is quite unknown and is likely to remain so until we discover the functions of the argentaffin cells. The frequent multiplicity of the tumours in the intestine shows that, whatever the carcinogenic factors may be they operate over the whole mucosa of the small bowel. In accordance with the presence of some argentaffin cells in the stomach, colon panetress and gail bladder occasional argentaffin cartinomas in these organs have also been described (Ashworth and Wallace) and they occur too in Meckel's discribed (ashworth).

(2) Number, site and appearance

Argentaffin carcinomas of the small intestine are often multiple. Of my 8

composed of gastric and Brunner's glands in a Meckel's diverticulum in a boy aged 16 years and were able to find records of only 3 other adenomas in diverticula Argentaffin carcinoma is the most frequent kind of neoplasm of Meckel's diverti culum (Stewart and Taylor, Price, Ashworth and Wallace)

(2) Umbilicus

Umbilical polypi, sinuses or cysts lined by intestinal or gastric epithelium derived from the vitello intestinal duct are not very rare (Nicholson, Peter I have examined an umbilical cyst 1.5 centimetres in diameter lined by gastric mucosa from a boy aged 2 years, and an extroverted polypus clothed by gastric mucosa, from a boy of 3 years, both present since birth, a collection of inflamed cysts 2 centimetres in total diameter, lined by columnar intestinal epithelium from a woman of 30 years and a cystic papillary tumour, probably of urachal origin (Case VI. Chapter 28)

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58 and of the cases reviewed by Ariel 57 Males predominate Cooke's and Ariel's combined figures comprised 100 men and 73 women. Dockery and Ashburn's series comprised 8 men and 5 women, and 7 of my 8 necropsy cases were men.

(4) Spread and metastasis

Following infiltration of the bowel wall spread in the peritoneum may lead to fibrotic contraction and kinking of the gut Metastasis to the neighbouring

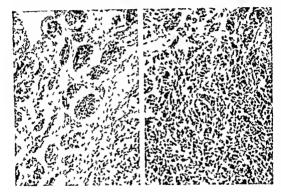


Fig. 187 — Case 1 Slightly anaplastic structure in a metastasis of argentalfin carcinoma in a lymph gland (× 105)
Fig. 188 — Case 1 Markedly anaplastic structure in a primary intestinal argentaffin carcinoma (× 105)

mesenteric lymph glands or to the liver frequently takes place (Figs. 186–187). Occasionally more remote metastases also appear e.g. in my Case V above, in the lungs kidneys adrenals retroperitoneal tissue subcutaneous tissue and perhaps in the gall bladder stomach and panereas (but these were possibly the sites of independent primary growths), in the brain skin and possibly in the panereas, in Case VI and in the kidney in Case IV Peritoneal dissemination is not common but was seen in the remarkable case described by Cope and Newcomb. For other instances of metastasis see the papers already cited and other references in my 1934 work (pp. 128.9).

TUMOURS OF VITELLO INTESTINAL TISSUES

(1) Meckel's diverticulum

Adenomas are very rare Schullinger and Stout saw a pedunculated adenoma

331 operation specimens, Dukes found the right sided parts of the colon affected in 75 and the left sided parts in 256, while during the same period there were more than 1 000 cases of rectal cancer. Raiford's series comprised 319 cancers of the rectum and 192 cancers of the colon, the latter including 67 of the caecum and ascending colon and 72 of the descending or sigmoid colon. The transverse colon and the hepatic and splene flexures are the least common sites.

(5) Multiple carcinomas

Multiple carcinomas of the large intestine may occur in the same segment or in widely separated parts of the bowel (Norbury Gordon Taylor, Dukes) My necropsies included, in addition to Cases I II and IV, the following combinations of sites of multiple growths in which the possibility of spread or metastasis from one site to the other could be evoluded (i) caccum and sigmoid,

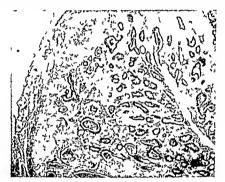


Fig. 189 -Adenocaremoma of colon in a rat (× 50)

(u) hepatic ficxure spienic ficxure and descending colon (plus multiple polypi), (iii) 3 separate carcinomas (and a polypus) in the sigmoid, (iv) sigmoid and rectum Dukes found multiple foci of origin in 29 of 1,000 cases of rectal carcinoma

(6) Intestinal carcinoma in animals

Like gastric cancer intestinal cancer is rare in all mammals except man Wells et al (1938) have reviewed the few reported examples in the mouse rat, cat, dog lion, ox, horse, racoon and dasyure, as well as the more frequent reports of the disease in birds. Intestinal carcinoma in mice occurs mainly in the prolapsed rectum and is more often squamous celled than adenocarcinoma. In 1935-I described two mucoid adenocarcinomas of the colon in rats, with metastases in lymph glands in both cases (Fig. 189). Schlotthauer reported a mucoid

CHAPTER 23

CARCINOMA OF THE LARGE INTESTINE

THE MAIN subject of this chapter is the common adenocarcinoma Benign epithelial tumours are considered in relation to cancer, and tumours of the appendix and anus are described separately in the last sections

FREQUENCY AGE SEX SITE AND SPECIES INCIDENCE

(1) Frequency

In Great Britain, Australia and some other countries mortality and hospital statistics show that carcinoma of the large bowel is only a little less frequent than carcinoma of the stomach. Thus, in Victoria in 1940-42, 1,534 deaths from cancer of the intestines were recorded as against 1720 from cancer of the stomach and my proved necropsy cases included 190 of carcinoma of the large intestine and 227 of carcinoma of the stomach. In communities where gastric cancer (q v) is unusually frequent, intestinal cancer accounts for a correspondingly lower proportion of all cancers, though it is still one of the commonest tumours in most countries.

(2) Agc

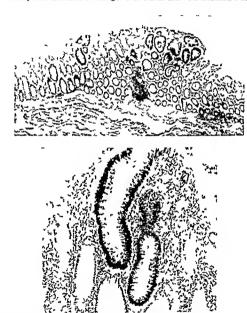
The greatest number of patients is in the sixth decade. The mean age in Hayden and Shedden's series of rectal cancers was 57 for men and 49 for women and in Dukes's (1940) series of 1000 rectal cancers 59 for men and 55 for women. The mean age of my 190 necropsy cases was 60. The discuss is rare under 30 years of age but has been seen in children e.g. in a boy of 13 years by Oglivie, and in a grid of 9 by Webster, who gives other references. Carcinoma supervening on familial polyposis often occurs in the second third or fourth decades. my second youngest necropsy case, a male of 24 years, was of this kind (see Case I below).

(3) Sex

Men are more often affected than women in a proportion between 3 2 and 2 1 in most series, e.g. 114 men and 76 women in my necropsy series. In Raiford's series the sex ratio was 2 1 for colonic cancer and nearly 3 1 for rectal cancer. The 1,000 rectal careinomas recorded by Dukes were from 650 men and 350 women. Hayden and Shedden's cases of rectal cancer comprised 179 men and 124 women. Dukes (1945) points out that cancer of the proximal end of the colon is more common in women than in men but that cancer of the pelvic 'colon and rectum is much commoner in men than in women.

(4) Site

Carcinoma increases in frequency from the proximal to the distal parts of the large intestine the rectum being the most frequent site of all. In a series of Case II — History — A woman aged 50 years had had intermittent diarrhoea for 30 years the motions usually being fluid and sometimes streaked with blood. Following recent attacks of addominate look and vomiting signatioscopy had revealed polyposis and a fungating carcinoma of the upper rectum. Necropii showed multiple polyposis of the entire large intestine a large fungating carcinoma of the ileo-caecal onlice a fungating carcinoma 3 centimetres in diameter of the recto signoid junction and an indefinite area suggesting carcinoma in the transverse colon sections of which confirmed the presence of early adenocarcinoma extending into the muscle cost. No metastases were found



Figs 190 and 191—Case I Polyposis of colon showing multiple tumour foci in which the glands show cellular atypism and hyperchromatism (× 20 and 120)

(b) Carcinoma is often accompanied by polypi

This was so in 27 per cent of 79 necropsy cases examined by Stewart (1931) and in no less than 25 of 33 consecutive cases of rectal and sigmoid caremoma examined by Dukes (1926) In a consecutive series of 40 operation and necropsy

adenocarcinoma of the rectum with lymph nodal and omental metastases in a dog

CAUSATIVE FACTORS

(1) Intestinal polypi

The structure of the common intestinal polypi-papillomas and adenomasis too well known to require description. They consist of well differentiated glandular tissue like that of the colonic mucosa with however, varying degrees of distortion of the epithelium and crowding and hyperchromatism of the nuclei Farly tumours appear as small sessile nodules, larger ones develop strap like pedieles clothed by normal mucosa The tumours may be solitary, few many or innumerable. The rectum and pelvic colon are the commonest sites of solitary or few polypi and are often the most heavily affected parts in eases with many growths Patients with very numerous tumours-multiple polyposis-often give a family lustory of the disease, many examples of familial polyposis were recorded by Dukes (1930) and Lockhart Mummery and Dukes (1939) The disease may arise in several successive generations may be transmitted by either sex and affects males and females about equally The polypi are not congenital but usually commence to appear between the ages of 15 and 25 years what is inherited is therefore not polyposis as such but a special proneness of the colonic mucosa to neoplasia. No family tendency is apparent in cases with solitary or few polyor and these may develop at any age

All polyps of the large intestine—whether numerous few or single and whether familial or not—are predisposed to careinomatous change the predisposition being least in the solitary polypus and greatest in familial polyposis. Let us consider the evidence under three heads

(a) Familial polyposis terminates in cancer

Victims of familial polyposis are almost certain to die of carcinoma of the colon or rectum at an early age usually between 25 and 45 years. Dukes and Lockhart Mummery recorded many instances and the following case exemplifies the early development of carcinoma.

Case I—Histori—Patients mother died of intestinal carcinoma following polyposis his maternal grandfather died of distriboca his only sister had proved polyposis and was probably developing carcinoma when last heard of his only brother was healthy At the age of 10 years the patient began to suffer from diarrhoea which was at first attributed to coluis but later shown by skingrains and signoindoscope to be due to polyposis. This became steadily worse some clubbing of the fingers developed and he died at the age of 24 Necropus showed severe polyposis of the whole large intestine 4 separate areas of ulcrated carcinoma in the rectum the largest 3 centimetres in diarmeter metastases in neighbouring glands and periodenum many large metastases in the liver (8 860 grammes). Microscopy showed active anaplastic adenocarcinoma and also revealed innumerable tiny foci of adunoma or early adenocarcinoma in many parts of the colonic mucosi. (See Figs. 190 and 191 and compare with Lahm s.)

Not all cases of widespread polyposis are familial. The following is an example of this disease terminating in multiple carcinoma, in which there was no record of any family tendency.

It should be added that the "polypi" often mentioned in ulcerative colins are usually not true neoplastic polypi, but merely inflammatory polypoid projections of residual mucous membrane

(b) Diverticulosis or diverticulitis

This sometimes coexists with caremoma (references by Stewart, 1931), but it is probable that the association is wholly fortuitous. Diverticulosis of the distal part of the large intestine is common in elderly subjects, so that its coexistence with cancer is inevitable in a considerable proportion of cases.

(c) Other intestinal infections

Amochic and bacillary dysentery, tuberculosis, bilharziasis, etc, apparently do not predispose to cancer. In Egypt rectal cancer is infrequent despite the prevalence of bilharzial disease (Dolbey and Mooro, 1924)

(3) The possible presence of ingested caremogens

Possible sources of ingested carcinogenic substances have been discussed in Chapter 21 and it was suggested that if these are poorly absorbable they might be an effective cause of colonic cancer Dukes (1945) made a similar suggestion

If cancer of the colon is due to a carcinogenic agent present in the faeces its influence would certainly be greatest towards the distal end of the colon because of the slower passage and greater concentration of the intestinal contents Perhaps future research will succeed in identifying carcinogenic substances in the faeces

THE STRUCTURE AND GROWTH OF CARCINOMA

As in the stomach so in the bowel, careinoma may assume predominantly propoid, ulcerative stendite or diffuse forms. Microscopically most umours are adenocaremomas, often of well-differentiated columnar cell type, often too of papillary pattern and often mucus secreting. Diffusely infiltrating sphero lal-cell or signet ring cell tumours are uncommon. So also are very anaplastic growths devoid of glandular orientation of the cells. Squamous metaplasta L. rare Excluding the appendix (see below), the large intestine is a rare site of argentaffin careinoma (Stout., Ashworth and Wallace. Potter and Docter). It is possible that the tumour in Case III above was of this kind.

Polypoid carcinomas often attain a large bulk within the bowel while effecting only slight infiltration of the wall. Infiltrating and stenosing growths, however, soon extend through the muscle coats and invade the surrounding peritoneal and fatty tissues. Here veins are often invaded. Invasion of veins was demonstrated in 17 per cent of the surgical specimens of rectal cancer studied by Dukes (1940, 1944) and in 70 of 170 necropsy cases of rectal cancer studied by Brown and Warren. It is demonstrable rather less frequently with colonic growths.

Osseous metaplasia of the stroma occurs rarely in intestinal carcinoma (Dukes, 1939)

specimens of carcinoma of the large bowel which I examined carefully for polypi, these were found in 24—they were multiple in 18 and were usually in the neighbourhood of the main growth. These findings show that intestinal carcinoma commonly arises in a field of predisposed mucosa. A crop of adenomata arise from this sensitive field. (Dules) The extent of the potentially neoplastic field evidently varies greatly it may be restricted to a local segment, or it may involve the whole large intestine as in widespread polyposis.

(c) Carcinomatous change in progress in a polypus is sometimes observed

Swinton and Warren concluded that an origin from polypi was demonstrable in 14 per cent of 827 cases of colonic and rectal carenoma. I have seen careino matious change develop in a polyping which presented in the signoid colostomy opening of a patient with inoperable careinoma of the rectum. The following case showing carcinoma of a polypius very clearly, has other points of interest also

Case III - A woman of 46 years died of abdominal malignant disease of clinically undetermined origin the chief symptoms of which had been recent rapid enlargement of the liver jaundice and emacration Necropsy -The sigmoid colon contained a polypus 1.5 centimetres in diameter with a narrow pedicle clothed by normal mucous membrane and a crateriform ulcer I centimetre in diameter on its summit. The meso-colon close to the base of the pedicle contained a mass of secondary growth in lymph glands 2.5 centimetres in diameter. The liver weighed 9 pounds and contained many large metastatic tumours and deposits were present in the portal and mesenteric lymph glands. The mucous membrane at the fundus of the gall blidder contained a nodule of tumour I centimetre in diameter. Small scattered podules of growth were present in the pancreas and spleen. The granual dura mater presented 2 tumour nodules each I centimetre in diameter. Many soft destructive areas of growth were present in the skull ribs and vertebrae Microscopy-In all situations the tumours were anaplastic spheroidal-cell growths with only slight sugge-tions of glandular formation. The structure somewhat recalled that of anaplastic argentaffin carcinoma but this diagnosis could not be claimed with certainty

(2) Inflammatory diseases

(a) Ulcerative colitis

This condition is occasionally followed by carcinoma. Thus caterinoma developed in 2.5 per cent of Brust and Bargen's 800 cases of colitis, but whether this proportion significantly exceeds that to be expected fortuitously is not clear from their paper since this gave no details of the age distribution of their cases. They mentioned however that carcinoma supervening on colitis was often found in relatively young patients. The following is the only example of this association that I have seen in about 30 necropsies on cases of ulcerative colitis.

Case II —A man of 42 years deed after having been under hospital treatment for ulcerative colus for many years. He had been treated with Bargen's vaccine and had had a long period with good health prior to the onset of the fatal illness. Necropy's showed severe ulcerative inflammation throughout the large intestine an ulcerated carcinoma of eculiar in diameter in the signoid colon and a separate stenosing carcinoma in the rectum. Microscop's showed both tumours to be adenocarcinomas involving all coats and accompanied by deposits in neighbouring lymph glands. A section of the colon in another part unexpectedly revealed a third area of early adenocarcinoma invading the muscle.

119 ounces Case III above exemplifies massive hepatic metastasis from a very small primary growth

(b) The lungs

The lungs contain secondary growths in about one fifth of fatal cases

(c) Other organs

Other organs, most often the adrenals, kidneys or bones, are affected in about 10 per cent of cases (Brown and Warren, Willis, 1941)

CARCINOMA OF THE APPENDIX

In 1906 Rolleston and Jones recepted and reviewed 42 previously reported cases of primary cancer of the appendix. They found these to be of two distinct types—the columnar celled like that of the large intestine and the spheroidal-celled, the latter being the tumour later designated "carcinoid" or argentaffin carcinoma—Uthlein and McDonold distinguished three kinds of appendical cancer—the carcinoid type, the cystic type producing pseudomyxoma peritone, and the colonic type—and estimated the relative frequencies as 89, 8 and 3 per cent respectively—It is, however, debatable whether the appendical lesion responsible for pseudomyxoma is usually truly neoplastic or only an obstructive mucocele—I have discussed this question, with references, elsewhere (Willis, 1934)—Here we will consider only the two undoubted types of carcinoma of the appendix, argentaffin carcinoma and adenocarcinoma of colonic type

(1) Argentaffin caremoma

This is by far the commonest tumour of the appendix. It is most often situated at or near the tip, and appears as a hard mass of yellowish issue usually only 1 or 2 centimetres in diameter which may appear well defined or may infilirate the appendical wall without clear demarcation. Partial calcification of the growth occasionally occurs. Most of the tumours are discovered only meidentally at operations for appendicitis or at necropsy. In their number, and their age and sex incidence they differ from the similar tumours of the small intestine (q v). The appendical tumours are usually single, only rarely multiple. They are discovered at ages ranging from 12 to 70 years, but most of them are found during the second and third decades the average age of the cases reviewed by Rolleston and Jones was 24. I have examined 11 specimens from patients ranging from 14 to 63 years old, with a mean age of 34 years. The sexes are nearly equally affected but in some series there has been a predominance of females, my specimens were from 4 males and 7 females.

Malignancy and metastases

Although the appendical argentaffin carcinomas are less dangerous than the enteric ones, there is no justification for the term 'carcinoid'. The growth often infiltrates the wall of the organ and reaches its peritoneal surface (Fig. 192) and there are many recorded cases with metastases in peritoneum lymph glands, liver and elsewhere (see references by Stewart and Taylor, and Willis. 1934)

METASTASIS OF CARCINOMA

(1) Metastasis by lymphatic channels

Careful dissection and microscopical study reveal regional lymph nodal metastrises in the majority of cases, e.g. in 62 of 100 operation specimens of rectal cancer described by Gabriel et al. in 505 of 1,000 operation specimens of reported by Dukes and in 28 of 46 cases of colonic cancer described by Coller et al. The first glands to receive metastases are usually but not always those neriest the primary growth, metastasis then takes place to more remote glands. Glands which appear to the naked eye to be unaffected may be found microscopically to contain metastases but more often enlarged glands thought to be cancerous are found to show inflammatory changes only. As with carcinoma of other organs the presence or absence of lymph nodal metastases is a major factor in prognosis. Gabriel et al recorded the following percentages of 5 year survivals following excision of cancer of the rectum when the tumours showed no extensions to the perirectal tissues 91 per cent. When the tumours had spread directly to the perirectal tissues but were unaccompanied by glandular metastases, 64 per cent. When glandular metastases were present, 16 per cent. For further details regarding lymphatic metastasis and prognosis see Dukes (1944).

Advanced intestinal carcinoma often shows tumour deposits in many groups of abdominal lymph glands—and it is one of the three commonest tumours to invade the thoracic duct—being surpassed in this respect only by gastric and uterine carcinoma

(2) Transperitoneal metastasis

Peritoneal dissemination is present in about 20 per cent of fatal eases of cancer of the large bowel. Anson saw a case of carcinoma of the caccium large pelvic deposits of which simulated primary rectal cancer.

Ovarian metastases occur in about 5 per cent of fatal cases and they have often simulated primary ovarian disease (Willis 1934). They are usually of adenocarcinomatous type and may be papillary cystic or mucoid they are rarely of Krukenberg type.

(3) Metastasis by the blood stream

(a) The liver

The liver contains secondary growths in one third or one half of fatal cases of in 31 of my 59 necropsies and in 57 of 170 in Brown and Warren's series of my 31 cases with hepatic deposits 11 had no other metastases. Goligher found that of 31 cases who had died a few days after excision of the rectum and whose livers had been thought clear of metastases at operation 5 cases were found it necropsy to have deposits deep in the liver. Very small primary growths in the bowel may produce gigantic chlargement of the liver the biggest recorded incr weight is 33 3 pounds (15 110 grammes) from a case of careinoma of the rectum (Christian). I have examined a liver weighing 11 000 grammes from a case of small annular careinoma of the sigmoid colon and kettle depicted a colonic growth 4 meh in diameter which had produced a liver weighing

(2) Adenocarcinoma

Rectal adenocarcinoma of the ordinary kind may of course extend to the anal canal and perineum. In the following case, however, an indenocarcinoma of peculiar type arose in the inal canal, probably from the intramuscular glands which are present there.

Case V—Histori—A man of 50 was admitted to hospital with symptoms of intestinal obstruction. He had had and sorteness for a year and more recent discharge and swelling Rectal examination disclosed ill defined induration around the anal canal. Ne ropsy showed two thirds of the circumference of the upper part of the anal canal to be diffusely inditirated by white growth which extended to the surrounding issue. There were no metastases. The signoid colon contained a single pedaniculated polypus 3 centimetres in diameter. Histology, (Fig. 193)—The mucous membrane of the anal canal is intact



Fig. 193 — Case V Adenocarcinoma of anal canal probably arising from the intramuscular glands $(\times 60)$

The sphuneter muscle is infiltrated by a carcinoma composed of broad epithelial columns, in part solid and in part containing actuar spaces surrounded by multiple layer of cells. The sigmoid polypus is a benign adenoma of the usual type.

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50 527

In most cases, however, removal of the appendix along with neighbouring lymph glands if these are affected is curative

(2) Adenocarcinoma of colonic type

This is a rare tumout in the appendix Rolleston and Jones reviewed 6 reported cases, Uillein and McDonold described 5 cases Phillips and Isaac one case, and I have seen 2 examples The tumours share the age incidence,



Fig. 192 -Inhitration of muscular coat by argentaffin carcinoma of appendix (× 120)

structure and behaviour of their colonic counterparts. Mucus secretion is often conspicuous. It should be noted here that caceal carcinoma may invade the appendix or may cau e obstructive appendicitis (Parker and Rosenthal Gordon Taylor.

CARCINOMA OF THE ANUS AND ANAL CANAL

(1) Epidermoid carcinoma

Gabriel has given a good account of 55 cases of this disease, which in its structure and behaviour generally resembles the epidermoid carcinomas of the skin. The mean age of Gabriel's cases was 62 and there were 27 men and 28 women. There was however a decided difference between the sexes as regards the initial sites of the timours. Those starting in the anal canal affected 23 women and 3 men while those of the anal margins affected 24 men and 5 women. Metas / lasis occurs mainly to the inguinal lymph glands, but the intrapelvic glands also may be affected.

CHAPTER 24

CARCINOMA OF THE LIVER

USEFUL early reviews of the pathology of primary carcinoma of the liver include those of Weigert (1876), van Heukelom (1894). Eggel (1901), Wegeln (1905), Goldzieher and Bokay (1911) and Winternitz (1912), and more recent accounts, those of Counsellor and McIndoe (1926), Fox and Bartels (1928), Strong and Pitts (1930), and Stewart (1931). In this chapter, benign epithelial tumours of the liver are considered in their relation to carcinoma. Embryonic carcinoma of the infant's liver is described in Chapter 60.

I have studied the following 15 necropsy cases of hepatic carcinoma

| Case No | Sex age | Description | Histology | Metastases |
|------------|-------------------|--|---|---|
| 1 | M 62 | Main growth 9 cents metres no currhosis | Liver-cell careinoma | Lymph glands liver peri- toneum lungs kidneys adrenals pancreas gastric and intestinal mucosa gall bladder thyroid brain many bones |
| 11 | F 61 | Single growth in cirrhotic liver | Liver-cell carcinoma | None |
| 111 | F 67 | Single tumour replacing I lobe no cirrhosis | Liver-cell carcinoma | Peritoneum |
| īV | M 60 (Chinese) | Main growth 15 cents metres in currhotic liver | Liver cell carcinoma (+adenocarcinoma) | Liver |
| v | M 71 | Multiple with haemo chromatosis | Liver-cell carcinoma | None |
| Vi | M 61 | Multiple with haemo chromatosis | Liver-cell carcinoma | None |
| VII | M 61 | Multiple with haemo chromatosis | Liver-cell carcinoma | None (portal ve invaded) |
| VIII | F 41 | Large tumour no cirrhosis | Adenocatcinoma | Lymph glands liver per toneum ovary bon (with paraplegia) |
| ix | M 64 | Huge tumour in spirit drinker without cirrhosis | Adenocarcinoma | Liver (with multip invasion of portal ar hepatic veins) Tumo emboli in lungs |

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necropsy cases 58 Highly susceptible coloured peoples suffer at earlier ages, Berman found that 83 per cent of Bantu patients were 40 years old or less, 44 per cent being in the third decade



Figs 194 and 195 - Liver-cell tumours of dogs (× 120)

(3) Sex

The disease is commoner in men than in women, the ratio ranging between 2 I and I2 I in various recorded series My 15 necropsy cases comprised 10 men and 5 women. In the Bantu, Javanese, Chinese and Japanese also there is a marked predominance of males.

| Case No | Sex age | Description | Histology | Metastases |
|------------|------------|---|----------------------|---|
| х | F 53 | Huge growth no cirrhosis | Adenocaremom2 | Hepatic veins invaded Metastases in lymph glands and lungs |
| ΧI | м 70 | Large tumour no cirrhosis | Adenocarcinom2 | Liver lymph glands peri toneum bones kidney |
| XII | М 73 | Main growth 20 cents metres no cirrhosis | Adenocaremom3 | Liver (with many veins invaded) lymph glands thoracic duct lungs adrenals |
| xIti | F 27 | Carcinomatous change in congenital cysts | Adenocarcinoma | Liver lymph glands lungs |
| χιγ | M 47 | Huge tumour no cirrhosis | Anaplastic carcinoma | Lymph glands thoracic duct liver lungs kidneys dura mater pentoneum (including hernial sac) |
| χv | M 56 | Main growth 20 centi metres no cirrhosis | Anaplastic careinoma | Liver, lymph gland |

Most of the cases have been reported elsewhere Nos V to VII in 1 paper on haemochromatosis in 1941 VIII to XI in a review of 500 necropsies in 1941 (Nos 341, 348, 349 and 421), No XIII in 1943 and No XIV in 1930.

FREQUENCY RACE AGE, SEX AND SPECIES INCIDENCE

(1) Frequency and racial incidence

Primary carcinoma of the liver is a diagnosis which can be established only by thorough necropsy, mortality statistics of this disease are therefore valueless this rate in white skinned peoples in whom it is found in 0.1 to 0.3 per cent of all necropsies (Stewart) or in about 1 per cent of necropsies on cases of malignant disease. My 15 cases occurred in a consecutive series of 1,400 cancer necropsies. In this series there were 505 cases (36 per cent) with secondary growths in the liver, thus secondary growths were 34 times as frequent as primary growths.

Hepatic cancer is much commoner in some of the coloured races especially the Bantu Javanese Chinese and Japanese (Stewart Bonne, Berman, Shear) Indeed it was the commonest malgnant tumour in Bonne's Javan necropsies and in Berman's Bantu cases. Of great interest is Berman's observation that there are marked differences in incidence in different tribes of the same race of the East Coast Bantu appear to be six times more liable than the South African Bantu. The high incidence of hepatic cancer in African Negroes does not appear in Negroes in America (Kennaway 1944). It is therefore not a racial character, but is due to environmental factors.

(2) Age

In Europeans carcinoma of the liser is commonest in the sixth decade. The mean age in Counsellor and McIndoe's compiled series was 61 5, and of my 15

MODE OF ORIGIN

While solitary carcinomas of the liver often appear to be of unifocal origin multifocal origin is equally clear in other cases, e.g. in my haemochromatosis cases, in the case of carcinoma arising in a developmental cyst (No XIII), and in Sanes and MacCallum s cases. When a tumour has invaded portal branch veins in the liver, however, it becomes difficult to decide whether multiple growths present have resulted from multifocal origin or intra hepatic metastasis. Stewart was inclined to interpret all multiple growths as due to spread and metastasis within portal veins. While fully endorsing the importance and frequency of such spread. I believe that genuine multifocal origin obtains in many cases

STRUCTURE

Two main types of structure are seen in carcinomas of the liver, (a) liver cell carcinoma or malignant hepatoma, and (b) adenocarcinoma of bile duct type or cholangioma. While many tumours fall into one or the other of these two classes, tumours of mixed structure also occur. I have seen several liver cell tumours which contained small areas of distinct columnar celled adenocarcinoma notably Case IV. Thus, while the distinction between hepatoma and cholangioma is useful, it is not a share one

(a) Liver cell carcinomia (Figs. 194-197) shows varying degrees of differentiation from a structure almost like normal liver tissue but without a proper lobular pattern to anaplastic growths with great cellular pleomorphism and much degen eration and haemorrhage. The botter differentiated growths often secrete bile and stain themselves yellow or green, even in their metastases (references, Willis, 1934). Anaplastic tumours with multinucleated giant tumour cells and much haemorrhage may mimic the structure of chorion carcinoma (Cruickshank, L Esperance).

(b) Cholangioma does not differ in structure or behaviour from the adeno carcinomas of the extra-hepatic bile ducts (a v)

METASTASIS

(1) Intra-hepatic portal metastasis

This occurs frequently Portal branch vens, sometimes the main ones near the porta, often show invasion of their lumina and extension of the growths along them (Fig 197), and metastatic growths are often present in the neighbourhood of the main growth or in distant parts of the liver. Stewart found portal vens invaded in 28 of 33 collected cases of liver-cell carcinoma, and in 5 of 11 cases of cholangiona, and I have referred to many records of invasion of portal or hepatic vens (Willis 1934). Imiasion of hepatic vens is the prelude to metastasis to the lungs. Tumours invading the inferior vena cava have sometimes extended up this vessel into the right utrium (Counsellor and McIndoe, Lochlein).

(2) Pulmonary metastases

These are recorded in about one fifth of fatal cases and were present in 5 of my 15 cases. As with other abdominal carcinomas the lungs may contain many intravascular tumour emboli without visible metastases (e.g. my Case IX)

(4) Hepatic careinoma in animals

This disease is not unusual in cattle and sheep (Feldman 1932) and in dogs, less common in cats horses pigs and other species (Feldman 1936). Winer and Schroeder 1940) Norris saw an adenocarcinoma of the liver in a rooster Rudduck and I studied the following liver tumours in animals

Dogs (1) Fox terrier, male aged 13 Multiple liver cell tumours largest

- 6 centimetres in cirrhouc liver (Fig. 194)
 (2) Airedale male, aged 14 Multiple small liver cell tumours in
- Airedale male, aged 14 Multiple small liver cell tumours in cirrhotic liver
- (3) Fox-terrier male aged 13 Solitary liver cell tumour 10 centi metres in diameter (Fig. 195)

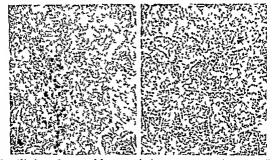


Fig. 196 — Liver-cell tumour of frog note alveolar structure and included pigrm-nt-cells (\times 60 and 120)

- (4) Collie female aged 12 Liver-cell tumour 15 centimetres in
 - (5) Mongrel male aged 15 Liver cell tumour 10 centimetres in diameter
 - (6) Foxhound male aged 7 Papillary adenocircinoma 15 centimetres in diameter with many metastases in liver, peritoneum and lymph glands

Persian cat aged 15 Adenocatemoma 10 centimetres in diameter Frog (Rana esculenta) adult Solitary tumour white but with black mottling

from included pigment cells of liver 3 centimetres in diameter, micro scopically a well differentiated hepatoma (Fig. 196)

CAUSATIVE FACTORS

(1) Cirrhosis

As a pre-cancerous lesion cirrhosis has been discussed by many of the writers

CHAPTER 25

EPITHELIAL TUMOURS OF THE BILIARY TRACT

In this chapter we will consider

- (a) Benign epithelial tumours
- (b) Carcinoma of the gall bladder
- (c) Carcinoma of the extra-hepatic bile ducts

BENIGN EPITHELIAL TUMOURS OF THE BILIARY TRACT

Polypoid and cystic cholecystitis (cholecystitis glandularis proliferans) bas often been misnamed "papilloma" or "adenoma", as in a paper by Shepard et al (1942). True pipillomas and adenomas of the bile channels are rare. In 1936 Kerr and Lendrum could find records of only 7 fully acceptable cases of pipilloma of the gall bladder to which Brown and Cappell (1937) added an eighth The papilloma of the gall-bladder described by Kerr and Lendrum was remarkable in that it consisted of intestinal epithelium, including Paneth cells, gobbet cells and argentaffin cells, and that it secreted large quantities of salt and water Multiple papillomas of the gall bladder, like that described by Brown and Cappell, were attributed by Kerr and Lendrum to transplantation, but a preferable interpretation is that they are, like the multiple papillomas of the intestine or stomach of multicentric origin. I have examined a pedunculated papilloma I centimetre in diameter in the gall bladder of a sbeep

CARCINOMA OF THE GALL BLADDER

- (1) Incidence, site, etc
- (a) Frequency

English and American surgical and necropsy records show that carcinoma of the gall bladder occurs with about one tenth the frequency of carcinoma of the smanch and constitutes about 3 per cent of fatal cases of carcinoma (Illingworth Mohardt, Kirshbaum and Kozoll) In my 1,060 necropsy cases of carcinoma (Table V, Chapter 5) there were 26 of carcinoma of the gall bladder

(b) Age

The mean age in various series ranges from 57 to 63 More than half the patients are in the sixth and seventh decades. The disease is very rare under 40 the youngest of my 26 necropsy cases was 44 years of age.

(c) Sex

Women are affected more frequently than men, m a ratio of about 3 or 4 to 1 (references by Mohardt) My necropsies comprised 18 women and 8 men

(d) Site and extent of origin

Many of the tumours are so extensive when first seen that their precise sites of origin cannot be specified but the neck and fundus appear to be more often

(3) Other metastases

Other blood borne metastases chiefly in the bones are less frequent Skeletal or other metastases may clinically simulate primary disease or may be the first signs of illness as in my Case VIII with paraplegia and Moon s case with patho logical fracture of the femur

Lymph nodal peritoneal or ovarian metastases occur in pethaps one quarter of fatal cases

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amounts, and further investigations of large pooled quantities of gall-stones or the liquid contents of cancerous gall bladders should be undertaken

(b) Cholecy statis

This is present in many cancerous gall bladders but it is doubtful if it itself is a significant causative factor. It may be only a concomitant of the associated gall stones, or may result from obstructive effects of the growth it elf. However, it must be admitted with Stewart, that a possible sequence of events in many cases may be cholecystitis, cholelithiasis, careinoma.

It has often been suggested that carcinoma may supervene on polypoid and cystic cholocystitis but this sequence, which by analogy with transformations well known in other regions is quite a probable one, has not and cannot be readily demonstrated. It would be well nigh impossible to distinguish microscopically between an area of proliferative cholocystitis with supervening carcinoma and an area of well differentiated adenocarcinoma. Proliferative cholecystitis with its invasion of the entire thickness of the gall bladder wall by the glands has itself often been mistaken for carcinoma e.g. by several of the experimentalists reviewed by Burrows. There is no evidence that the strawberry gall bladder is predisposed to cancer.

(3) Structure

The gross form of the tumours varies

The most frequent is the infiltrating scirrhous type leading to diffuse thickening of part or the whole of the wall and spreading to surrounding tissues

Less common are polypoid and papillary growths projecting into and distending the lumen

Combinations of the two types of growth are seen, and sometimes gelatinous change is prominent

Microscopicalli, most of the tumours are infiltrating adenocarcinomas of varying degrees of differentiation. Mucus secreting adenocarcinoma is quite common but diffusely infiltrating signet ring cell carcinoma is rare. Undifferentiated carcinomas also are infrequent. Squamous metaplasia is present in some degree in about 10 per cent of the tumours, and is sometimes prominent throughout. In my experience, however, it is never complete but is always associated with adenocarcinomatous structure. There is no evidence to support the statement sometimes made that the growths showing epidermoid metaplasia have arisen in areas of mucosa in which metaplasia had previously been present. The change takes place in the growths themselves, squimoid change is not seen in non-neolastic lesions of the rall bladder.

(4) Metastasis

L) mph elands contain deposits of growth in a high proportion of fatal cases e.g. in 18 of my 26 necropsies, and in 34 of 55 in Kirshbaum and Kozoll's series, the glands along the cystic duet and in the ports of the liver are the earliest affected. Cappell and Tudhope described a ease in which a small unsuspected carcinoma of the gall bladder had produced widespread metastases in lymph glands and had led to a diagnosis of "lymphadenoma or lymphosarcoma". The liver contains discrete metastases in more than one half of the cases e.g. in 16 of my 26 necrosises.

affected than intermediate parts. Multiple separate areas of growth are not unusual, I have seen several unequivocal examples, and there is no doubt that more thorough examination of gall bladders with early carcinomas would often show these to be of multicentrie or widespread and progressive origin. A frequent form of cancerous gall bladder with eutensive uniform thickening of the wall, resembling the leather hottle stomach may well be attributed as much to extensive origin as to extensive spread of the growth, and this interpretation is strengthened by frequent instances of widespread carcinomatous disease affecting the walls of the gall bladder and main bite ducts simultaneously (Willis 1942)

(e) Race and species

Carcinoma of the gall bladder occurs quite commonly in American negroes (Kirshbaum and Kozoll). It is recorded infrequently in some Oriental races e.g. in Java, where gall stones also are uncommon (Bonne). In animals cancer of the gall bladder has been seen occasionally in the ox. dog. and fout (Feldman)

2) Causative factors

(a) Gall stones

These have been present in from 60 to 100 per cent of cases in different series (Stewart Mohardt), they were present, or had been present in 24 of my 26 necropy cases. There is no doubt that the stones precede the growths in most cases and it is of interest that cancer may develop many years after removal of stones. 24 years in one of my cases (1942). The stones most commonly present in the cancerous gall bladder are of the multiple pigmented type. solitary pure cholesterol stones are also encountered but Stewart found that these did not occur with greater frequency in cancerous cases than in control cases.

The frequent association of stones with cancer of the gall bladder has led to many attempts to produce this disease experimentally in animals by inserting gall stones and other foreign bodies into the organ. These have included pebbles, suture materials, lanoline paraffin pitch tar cement pumice and tile fragments. The experiments were fully reviewed by Burrows (1933) who also carried out personal experiments with gall stones, plaster of Paris pellets containing cholesterol pellets containing dibenzanthracene and pieces of sponge soaked in fat containing dibenzanthracene (1933 and 1939). Burrows obtained inflammatory profilerations resembling human polypoid cholecystitis but no tumours and from his review it was clear that this had been the case also with the results of earlier workers, some of whom had claimed to have produced tumours. Nearly all the experiments of this kind have been on the guinea pig an animal which seldom develops spontrineous tumours and which is also refractory to the experimental production of skin tumours. Further attempts to produce cancer of the gall-bladder should be made on other species.

Hypothetically stones from cancerous gall bladders might well contain chemical carcinogens. Professor E L Kennaway and Dr I Hieger kindly examined several such stones which I sent them but found nothing distinctive spectrographically in extracts which also failed to produce skin tumours in mice However naturally occurring carcinogens might be present in very minute.

Kirshbaum and Kozoll's cases. In my 1942 series, none of the 15 cases of bile duct cancer had stones in the affected ducts, but in 3 cases the call bladder contained stones, and in all 3 cases of combined carcinoma of the ducts and call bladder stones were present in the gall bladder Cholecustitis and cholangitis are of doubtful causative importance in duct cancers

(3) Structure

Whether taking the form of diffuse thickening of long reaches of the ducts or annular stenoses or bulkier nodular growths, most of the tumours are infil trating scirrhous adenocarcinomis, occisionally with mucoid areas. Projecting papillary carcinoma is infrequent. I have not seen squamous metaplasia in any of my specimens, nor have I seen it described

(4) Metastasis

Metastases are less frequent than with carcinomas of the gall bladder, probably because early biliary obstruction proves fatal before the tumours have extended far Lymph glands were affected in 28 of Kirshbaum and Kozoll's 62 necropsies In my 15 cases (1942) metastases were present in lymph glands in 3 cases, in the liver in 3 in the peritoneum in 4, and in the lungs in 2 cases

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Other sites of metastasis include the lungs bones and ovaries, Foggie and Tudhope described a patient in whom the clinical and radiographic findings were those of primary cancer of the lung but necropsy disclosed this to be a metastasis from a carcinoma of the gall bladder

CARCINOMA OF THE EXTRA HEPATIC BILE DUCTS

(1) Incidence, site, etc

(a) Frequency

Contrary to the general impression of clinicians carcinoma of the main bile duets is at least as frequent as carcinoma of the gall bladder on the one hand and carcinoma of the panceras on the other. The belief that the pancreas is a much commoner site of cancer than the bile duets is due to misdiagnosis of many cases of cancer of the common duet as cancer of the head of the pancreas. Adequate necropsy study of the distribution of tumours in this region soon exposes this error. In a 5 year period during which 1 directed special attention to the sites of carcinomas of the bile passages and of the pancreas seen at necropsy 1 encountered 11 carcinomas of the gall bladder 3 of the gall bladder and bile duets 15 of the bile duets and 14 of the pancreas (1942). In Kirshbaum and Kozoll's necropsy series there were 55 carcinomas of the gall bladder 62 of the extra hepatic bile duets and 41 of the head of the pancreas. Like myself (Chapter 5 Table I) these workers found a high proportion of clinical misdiagnoses in this region in both thair series and mine carcinoma of the gall bladder and bile duets had been correctly disangued in only 22 per cent of cases.

(b) Age

The age distribution is about the same as for cancer of the gall bladder more than half of the patients are in the sixth and seventh decades and patients under 40 years are rare

(c) Sex

Unlike cancer of the gall bladder, that of the ducts is slightly more frequent in men than in women e.g. 17 men and 15 women in mw necropsies and in the ratio of 55 and 45 per cent in Kirshbaum and Kozoll's series.

(d) Site

Kirshbaum and Kozoll recorded 7 carcinomas of the cystic duct. 13 of the hepatic ducts 32 of the common duct and 10 of the papilla. In my 1942 study 10 of 15 duct cancers affected the common duct only 3 the hepatic ducts only one the common and cystic ducts and one the hepatic cystic and common ducts. In addition, as mentioned above there were 3 cases in which extensive cancer of all the main ducts coexisted with cancer of the pall bladder. Stenosing growths restricted to short segments of the bile ducts are most frequent in or just above the ampulla of Vater, and it is these growths that are often confused with carcinomas of the head of the pancreas.

(2) Causative factors

Gall stones are present in only a minority of cases e.g. in 31 per cent of

observed widespread panercatic changes which were structurally adenocarcinomatous but without metastases

(2) Causative factors and mode of origin

Nothing is known of the causation of pancreatic carcinoma. Inflammatory changes in the pancreas accompanying cancer are in most cases clearly secondary to duct obstruction caused by the growths. Neither pancreatic nor bilary stones are found with disproportionate frequency. Haemochromatosis does not predispose to carcinoma of the pancreas. There is no evidence that heterotopic pancreas, in the stomach, intestine or Meckel's diverticulum, is specially prone to tumour formation, though instances of carcinoma of heterotopic pancreas have occurred (see Nicholson's case referred to in Chapter 21)



Fig 201—Actuar type of adenocarcinoma The growth was an early one 4 millimetres in diameter, found in the fail of the pancreas at necropsy on a woman aged 73 (× 120)

Korpassy observed metaplassa with stratification of the epithelium of the pancreatic duets, mainly in elderly people but there is no reason to suppose this to be pre cancerous, as squamous metaplassa is rare in pancreatic carcinoma Haban described the multicentine or diffuse origin of papillary carcinoma in the duets

(3) Structure and growth

In the great majority of cases cancers of the pancreas are adenocarcinomas of varying degrees of anaplasia, undifferentiated tumours of spheroidal celled or diffusely cellular anaplastic types are uncommon Most of the adenocarcinomas are columnar celled and probably derived from the ducts Others display a small acunar type of structure reminiscent of the secreting tissue of the pancreas (Fig 201) Sharp separation of ductal and acunar growths, however, is not

CHAPTER 26

EPITHELIAL TUMOURS OF THE PANCREAS

EPITHELIAL tumours of the pancreas comprise

- (a) Benign cystadenomas
- (b) Carcinomas of duets and acini
- (c) Adenomas and carcinomas of islets of Langerhans

BLNIGN CYSTADENOMAS

These are well circumseribed rounded tumours sometimes small and discovered only incidentally at necropsy or operation, sometimes large enough to cause symptoms. The smaller tumours consist of a honeycomb of spaces, lined by columnar or cuboidal epithelium similar to that of the pancreatic ducts and containing mucinous secretion (Fig. 198). Large tumours also are often multi-locular but in some cases one cyst attains a great size and the others are compressed in its walls. Papillary growth of the epithelium is frequent. Examples of large beingin cystadenomas have been described by Carling and Hicks Janes, and Bowers et al., and of their malignant counterparts by Kennard (see also Case I below). Cystic tumours must be distinguished from polycystic disease of the pancreas a widespread change of developmental origin (Nygaard and Walters).

CARCINOMAS OF DUCTS AND ACINI

- (i) Frequency, age, sex, site and species incidence
- (a) Frequency

The proportion of clinical misdiagnoses in this disease is so high that the mortality figures are of little or no value (see Chapter 5). The only reliable sources of data for assessing the frequency and other properties of the disease are series of proved necropsy cases. There is little doubt that many cases called carcinoma of the head of the panceras at operation or even at necropsy, are really cases of carcinoma of the lower part of the bile duet (see Chapter 25).

Recognition of this confusion of the two diseases would result in a diminished number of tumours recorded as panereatic and an increased number recorded as bilary in origin. My necropsies included 42 proved cases of carcinoma of the panereas compared with 227 of the stomach. 190 of the large intestine and 58 of the biliary tract.

(b) Age

The highest numbers of cases occur in the sixth and seventh decades. Of Wallaus 330 necropsy cases 54 per cent were between 50 and 70 years old old and 73 per cent between 40 and 70 In Duff's scries of 50 necropsy cases the corresponding percentages were 52 and 72 The mean ages in Wallaus,

by growth and distended with mucus and tumour deposits were present in lymph glands along the course of the thoracce duct and in the left supraclavicular fossa. Liver and other abdominal organs were free from growth. The lungs were enlarged and heavy, weighed 64 and 55 ounces and showed widespread gelatinous infiltration partly diffuse and ill defined and partly as well defined patches up to 6 centimetres in extent. All the bronchi were filled with tenacious mucus. The hiar lymph glands contained gelatinous growths. Microscopy—The pancreatic growth was a well differentiated columnar celled adenocarcinoma. The lungs were infiltrated throughout by mucord adenocarcinoma consisting partly of columnar-celled growth which tended to line the invaded palinonary.



Fig. 203 — Case II Phagocytes accompanying the mucus produced by the tumour in the lung (\times 200)

rur sacs (Fig 202) and partly of mucmous lakes containing isolated tumour cells Accompanying the mucus in ar sacs and bronch were many phagocyte foam-cells and gain-cells (Fig 203). Moniha wa, present in the mucus. There was little or no rue pneumonic change. Diagnosis—Symptonless carcinoma of pancreas invation of thorace duct massive mucoid metastases in lungs especially occupying rur spaces growth of moniha in the mucus expectoration of mucus with moniha leading to false diagnosis of monihasis.

The amount of destruction of pancreatic tissue effected by cancerous disease varies greatly. Often the tumours are relatively small, occasionally the whole pancreas is replaced by the growth. Even massive replacement of the pancreas does not necessarily produce diabetes for the islets of Langerhans may long remain intact in areas of tumour which has destroyed all the external secretory tissue. Sometimes however, extensive cancerous disease does produce diabetes, as in an interesting case which I have described elsewhere (1941). Marble has discussed the association of diabetes with malignant disease generally, neluding 33 crises of pancreatic careinoma.

(4) Metastasis

Limph glands contain tumour deposits in most fatal ca es, e g in 30 of my

practicable The possible occurrence of argentaffin carcinoma in the pancreas 'should be borne in mind (see below)

Most of the pancreatic adenocarcinomas are solid growths with no special characters. But a few tumours show prominent mucoid or cystic changes. Mucoid carcinomas have been reviewed and described by Hemken, and papillary cystadenocarcinomas by Kennard. The following case of cystic carcinoma is noteworthy.



Fig. 202 — Case II Metastatic mucoid columnar-celled adenocarcinoma occupying pulmonary directi (\times 120)

Case 1—History—A woman 45 years old had first noticed a left upper abdominal mass 2 years previously. Exploration showed this to be a single large cyst of the tail of the pancreas with thickened walls adherent to surrounding parts. The contents was turbed brownish fluid with a high distase content. Averagely, showed the tail of the pancreas replaced by a well-defined rounded cystic tumour 10 centimetres in diameter partly thin walled and partly, thick walled with nodular misses of growth sprouting into the cavity. The head and neck of the pancreas contained several small ill-defined separate areas of solid white growth. Multiple metastatic tumours were present in neighbouring lymph glands liver lungs and kidneys. Microscopy—The cystic growth showed well differentiated papillary cystudenocarcinoma with some cellular anaplastic areas. All other tumours were of the latter kind.

The following interesting example of mucoid carcinoma is notable also because of a peculiar error in diagnosis

Case II—History—For some months a man of 62 had suffered from cough with abundant mucoid sputum from which monila was repeatedly cultured. There were signs and X-ray appearances of widespread patchy pneumonic change and the clinical diagnosis was pulmonary monilasis. Acropin showed an ill-defined carcinoma 3 centimetres in diameter in the body of the pancreas with deposits in surrounding lymph glands and some diffuse infiltration of the retroperitorical issues. The cisteria chil was enveloped

ADENOMAS AND CARCINOMAS OF THE ISLETS

(1) Islet adenomas

Islet adenomas are not rare. They appear as small circumscribed nodules discovered incidentally at necropsy (Korpassy, and Fig. 206), or are clinically



Fig 205—Case III Microscopic infiltration of the meninges in a cerebral sulcus (× 35) Fig 206—A small islet adenoma found at necropsy on a woman aged 67 (× 120)

important in producing hyperinsulmism (Whipple and Frantz, Frantz, Haines) Even when productive of symptoms, most of the tumours are less than 2 centimetres in diameter, but larger tumours, up to 500 grammes, have been seen 42 necropsies Peritoneal dissemination also occurs frequently, especially from cancers of the body and tail

The liver contains metastrises in about two thirds of fatal cases e.g. in 192 of Wallau s 330 and in 29 of my 42 necropises. The point of entry of the tumour into the portal circulation is often demonstrable in the splenic or portal ceris or their main tributaries (Duff). Other sites of blood borne metastases are less frequent the commonest being the lungs which are affected in about one fifth of fatal cases. In a remarkable case reported by Hegler and Wohlwill there were splenic enlargement rarefying lesions in bones seen in skiagrams and



Fig. 204 —Case III Metastatic adenocarcinoma of vertebra (× 120)

multiple subcutaneous lesions thought to be blistomycotic necropsy disclosed an adenocarcinoma of the tril of the panereas with metastases in bone marrow and subcutaneous tissues in which pronounced fat necrosis suggested that the tumour cells had continued to secrete digestive ferments. Metastases in the brain though infrequent may attain a large size and may simulate primary cerebril disease (Foot et al. Dickson and Rejnell. Willis 1941). The following case showed unusural metastases.

Cate III—Male 64. Clinical disensity pulmonary fibrous. Accrops:—Carcinoma, of head of pancreas 4 centimetres in diameter not involving bil, duct with deposits in neighbouring lymph glands and in personeum. Multiple metadases in hier Jurgs both ribrands thyroid and several vertebrate. Brain showed slight milky opacities of pia-archinoid and felt slightly slimy but no definite metastasys found. Microscip (Figs. 24 and 205)—Well-differentiated adenocarcinoma in all situations diffuse microscopic inflitration of manipres by growth with shight extinsions into brain.

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Their most frequent site is the tail but they may be found in any part of the pancreas and multiple tumours occur. Although well defined to the naked eye adenomas are often not encapsulated but show marginal infiltration of the surrounding pancreatic tissue. Sharp microscopic distinction between beinging and malienant islet cell tumours is not possible.

(2) Islet carcinoma

This was first described by Wilder et al (1927) whose patient had suffered from hypoglycaemic attacks and who demonstrated the presence of insulin in the hepatic metastases as well as in the primary tumour at necropsy. Duff referred to 6 subsequent reports of islet-cell carcinoma and recorded a case with wide spread metastases. Three of these cases had shown evidence of hyperinsulinism, proving their nature. Frantz, Finn et al., Gray and others have reported additional cases of insulin secreting islet cell carcinomas with hepatic metastases. Caution is needed however in identifying 'islet cell carcinomas' from their structure alone when no clinical or chemical evidence of insulin secretion is demonstrable. In structure a disorderly islet cell tumour might closely resemble a disorderly argentaffin carinoma, such as my case (No. 330) of diffuse carcinoma first described in 1936 and later (1940) identified as of argentaffin type. Frantz properly emphasized that islet adenomas and carcinomas are not sharply separ able, islet tumours form a single group with a wide range of behaviour, slowly growing localized tumours predominating.

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Adenoma of islet cells with hyperinsulinism "

2 centimetres or more in diameter, but most of them are less than 1 centimetre. They are frequently multiple, and are often present in both kidneys. The kidneys almost always show distinct evidence of arterioscletotic or chronic nephritic.



Fig. 208 -Adenoma of kidney, papillary type with granular calcification (x 120)

changes Adenomas are found chiefly in middle-aged or old people and are uncommon in youth my specimens came from 26 men and 15 women, whose mean age was 52 years

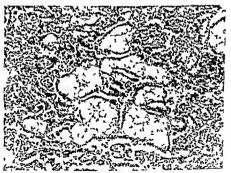


Fig. 209 -Adenoma of kidney, collections of foam cells in the stroma (x 120)

(2) Structure

Figs 207 210 depict some of the commoner appearances Many of the tumours show a predominant intra cystic papillary structure, justifying Newcomb's

CHAPTER 27

ADENOMA AND CARCINOMA OF THE KIDNEY PARENCHYMA

EPITHELIAL tumours of the kidney are of the following distinct types

- (a) Adenomas and carcinomas of the uninferous tubules of the adult kidney, the subject of the present chapter
- (b) Papillomas and carcinomas of the transitional stratified epithelium of the renal pelvis to be described in the next chapter
- (c) Embryonic tumours or nephroblastomas of the foetal or infant kidney (see Chapter 60)

ADENOMA OF THE KIDNEY

(1) Frequency, number, distribution, etc

In necropsy work it is common to discover small nodules of various kinds in the kidneys. Most of these are adenomas fibrous medullary nodules small evitys with inspissated contents small leiomyomas nodules of adrenal cortex and small lipomas, in that order of frequency. With the exception of the rather common small fibrous nodules usually 3 or 4 millimetres in diameter found in the medulla of both young and old kidneys, nearly all of the foregoing are cortical in position. Microscopical examination is necessary to distinguish the several kinds of nodules from one another. Most of them prove to be cortical adenomas



Fig 207 -Adenoma of kidney papillary type (× 120)

These have been well described by Nicholson (1923) Newcomb and Trinkle with whose findings my own are in substantial agreement

Cortical adenomas of the kidney appear as well defined but often not encapsu lated rounded or somewhat pyramidal nodules usually yellow in colour and either solid or cystic. They vary in size from just visible dimensions up to

to say-just as in the breast, thyroid and liver it is often difficult to distinguish sharply between hyperplasia and neonlasia

Are adenomas related to caremomas? Anyone who has examined and compared the structure of these tumours will have no hesitation in joining Newcomb and Trinkle in a strongly affirmative answer Indeed, a sharp separation of adenomas and caremomas is not possible. Some adenomas show a structure indistinguishable from that of caremomas, and it is purely a matter of opinion whether we regard such tumours as atypical adenomas or its young caremomas which we happen to have discovered before they have metastasized. Many an

adenoma "found incidentally at necropsy differs not one whit from some of those small symptomiess carcinomas which have produced precocious metastases. Renal tumours, like other tumours, differ in their individual rates of growth, invasiveness and metastasizing proclivities. It is proper that those tumours which for long periods grow slowly, attrin a uniform highly differentiated structure and faul to spread should be called 'adenomas' to distinguish them from their more active fullows and it is of course true that most of these more active growths show plain signs of their activity in their size, structure and invasiveness. But there are no structural circteria which will permit clear cut separation of the black sheep." from the other members of the family

CARCINOMA OF THE LIDNEY

Excluding the tumours of the renal pelvis and the embryonic nephroblastomas, all of the remaining malignant epithelial tumours of the kidney form a single group. Attempted sub division of this group of common renal tumours arises either from antiquated views on histogenesis or from ignorance of the wide range of structure to be seen in the group and even in one tumour. "Growitz tumour"

hypernephroma' clear celled careinoma', 'solid-celled careinoma', etc are not separate kinds of tumours, but merely names which have been given to the single entity carcinoma of the renal parenchima. In what follows then, we deal with this entity without regard to iritificial distinctions, the falsity of which will appear in the discussion. Of the many papers on the origin, structure and behaviour of renal careinomas those of Sudeck Manasse, Albrecht Stoerk, Zehbe, Ipoen Wright and Nicholson are of special value.

(1) Incidence and causation

(a) Incidence

The incidence of renal carcinoma is difficult to assess, because of the frequency with which clinical and pathological misdagnoses have been made in this disease Microscopically proven necropsy series are the only reliable source of data for estimating the true frequency and other properties. Of my 1060 carcinoma necropsies (Table V Chapter 5), renal carcinoma accounted for 27 cases, 12 21 per cent. this was about one tenth of the frequency of gastric carcinoma and one third the frequency of nulmonary carcinoma.

(b) Age

The highest proportion of cases is seen in the sixth decade and about 50 per cent are in the fifth and sixth decades. The mean age at death of my 27 necropsy

designation 'papilitérous cyst adenoma' others show tubular or solid areas, and all kinds of structure may be seen in one nodule. In many tumours the epithelium consists mainly of small solid cubical cells but in other tumours the cells are larger, vacuolated or foamy, and closely resemble those of the clear celled renal carcinomas, and solid and clear cells may occur in one tumour Common structural features attributable to secondary changes include accumula tions of phagocytic foam cells in the stroma of the tumours, granular calcification, intri cystic haemorrhage, and deposition of blood pigments in the epithelial cells and in the stroma

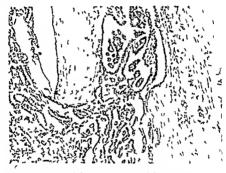


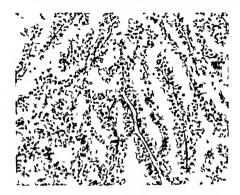
Fig. 210 —Adenoma of kidney extension through fibrous capsule. (× 120)

Many small adenomas show no encapsulation, their marginal elements mingling with the neighbouring renal tubules. Other nodules show thick fibrous capsules but these are rarely if ever complete and at one or more points extensions of the growth through the capsule mingle with the surrounding kidney tissue (Fig. 210).

(3) Origin, growth and relationship to earcinoma

From the study of early adenomas it is clear that these arise from the epithelium of hyperplastic convoluted tubules and cysts in damaged kidneys (Stoerk, Nicholson Newcomb Trinkle) Continuity of adenomatous epithelium with renal tubules can often be traced and the genesis of the growths appears clearly to involve progressive transformation of tubules into tumour, a process which accounts largely for the interningling of tumour and renal tissue. Whether adonass are truly neoplastic from their inception or whether they arise first as focal compensatory hyperplassis which later become neoplastic it is difficult.

of renal adenocarcinoma by subcutaneous injections of β anthraquinoline (Sempron) and Morelli, Chapter 4) supports the suspicion, plausible also on general grounds, that cancer of the kidney may be due to absorbed chemical carcinogens acting selectively on the renal epithelium during their exerction Close scrutiny of the occupational, dietetic, and drug histories of victims of the disease might lend to discovery of such carcinogens. The higher incidence of renal cancer in males increases the suspicion of occupational factors in causation



Fio 211 - Clear-celled carcinoma, well differentiated tubules (× 120)

(2) Gross structure and growth

(a) Naked eye appearances

(d) Naked eye appearances

The naked eye appearances of renal carcinomas are too well known to need description. Their seeming circumscription and expansive lobular appearance, their variable bulk from small adenomalike tumours to huge masses weighing many pounds their yellow or orange colour rendered all the more variegated by areas of fibrosis, necrosis, haemorrhage and cystic changes, and their grossly polypoid invasion of the renal pelvis and of main vens are all familiar features. Parts of the tumours which consist, not of the characteristic clear cells, but of more anaplastic cellular growth or of solid celled papillary adenocarcinoma, appear white and white and orange yellow areas often occur in one tumour. Cysts often arise irregularly from degeneration or haemorrhage, but in other cases they are an integral part of the habit of growth of the particular tumour, parts or the whole of which may assume a regular honey combed or polycystic pattern. Such cysts may attain large sizes and thick fibrous walls, in which calcification visible in skiagrams may occur.

cases was 58 years. The disease is rare under 30, my youngest cases were 29, 30 and 32 years of age. Nicholls reported clear celled pupillary admocarcinoma in an infant of 22 months.

(c) Sex

In almost all recorded series there is an excess of males over females, the ratio ranging between 3 2 and 5 1. Thus Newcomb a necropsy cases comprised 19 men and 5 women, and mine 23 men and 5 women.

(d) Race

There are no reliable comparative figures but renal earcinoma occurs in Indians Chinese, Negroes, and other native races (Cooray, Quinland and Cuff, and other references Chapter 5)

(e) Site

Young tumours are invariably situated in the cortex, and the relationships of some large tumours also to the surrounding fidney tissues indicate their cortical origin. The tumours arise in any part of the cortex and the right and left kidneys are affected with about equal frequency. Bilateral growths occasionally occur (Forsythe Beilin and Neiman) but of course metastasis in one kidney from a carcinoma of the other might simulate bilateral new growths. Exley and Hotchkiss reported carcinoma in a supernumerary kidney.

(f) Renal carcinoma and adenoma in animals

Nicholson (1913) described a transplantable careinoma of the rat s kidney and give references to reports of renal tumours in mice. Renal careinoma also occurs occasionally in dogs (Feldman Haigler). I have examined a renal careinoma from a dog in which both primary growth and metastases in lymph glands and lungs showed well differentiated papillary structure and granular calcification and closely resembled the cortical adenomas of the human kidney. Renal adenocareinomas resembling those of human beings occurred in several rhesus monkeys in one family described by Ratcliffe. Nieberle and Cohristepied a large adenoma of the kidney of a horse and stated that such tumours often attain a huge size may be papillary or cystic and may become careinomatous. The renal adenocareinomas of frogs studied by Lucke were referred to in Chapter 6 (For the embryonic renal tumours of pigs, rats rabbits and birds see Chapter 60).

(g) Causative factors

Save for the clear relationship of carcinoma to adenoma and for the almost invariable origin of the latter as hyperplastic foci in dimaged kidneys nothing is known of the causation of renal carcinoma. Carcinoma in a granular kidney is often associated with adenomas of other parts of the kidney. It is probable that only some circinomas arise from pie-existing adenomas for in only a proportion of cases do cancerous kidneys show evidence of nephritis or arterio sclerosis such is usually accompany adenomas. The experimental production

parts of clear celled tumours This is probably the most healthy type of differ entiated structure, and the lipoid accumulation in the more abundant clear-celled

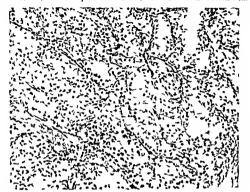


Fig 213—Clear celled executions primary growth in kidney from same case as Fig 218 (× 120)



Fig. 214—Clear celled carcinoma—trabecular pattern in a subcutaneous metastasis in the arm $(\times 120)$

areas is to be regarded as a degenerative process comparable with the lipoid change in the renal epithelium in other pathological conditions, e.g. in chronic

(b) Invasion of main veins

Invasion of main veins is frequent and can be found if searched for in the majority of cases Elsewhere (Willis 1934) I have given references to many examples of intravenous spread of renal carcinomas which in some cases have extended up the inferior vena cava into the right chambers of the heart (Polayes and Taft) McDonald and Priestley have given good illustrations of venous invasion and have shown how this influences prognosis

(3) Microscopic structure

The microscopic structure of renal carcinomas (Figs. 211 216) is very diverse including the following variants



Fig. 212 -- Clear-celled caremoma - Iubular and papillary structure (× 120)

- (a) Most distinctive of course is the vacuolated or clear celled type of growth which is characteristically found in the healthy orange yellow parts of the tumours of and which may permit prompt identification of the nature of a tumour from a glinee down the microscope. This clear celled type of growth may show distinct tubular or papillary glandular structure or it may be compressed together and devoid of recognizable luminar presenting in section the appearance of plant tissue. Thorough search however will disclose glandular formation in parts of most tumours. The clear celled appearance is an artefact due to the presence in the cells of quantities of doubly refracting liphod material which is dissolved out by the fat solvents used in preparing paraffin sections but which is readily demonstrated in frozen sections or extracts of fresh tumour tissue. Glycogen also is present in the clear cells.
- (b) Solul celled papillary adenacarcinama reminiscent of the common form of structure of the renal adenomas is less plentiful but is often to be found in

pathologists, has been specially discussed and exemplified by Loening, Schminke, Brandt, Schaffhauser, and Willis (1932)

(d) Highly vascular and haemorrhagic tumours also used to be a source of confusion in histological diagnosis Haemorrhages into tubular or cystic glandular structures are very common, and produce appearances which were thought to denote a vascular origin of the growths, to which such names as 'perithelioma', 'endothelioma' and 'angio sarcoma' were applied There is, of course, no justification for such mistakes nowadays

It is important to recognize that these several varieties of structure do not denote different types of tumour, but are often to be found together, in varying proportions, in individual tumours. The more thoroughly the tumours are examined the more fully it will be appreciated that sub-division of the group is unustified, and indeed impracticable.

(4) Histogenesis

To anyone familiar with the structure of renal careinomas and adenomas it seems incredible that Grawitz's hypothesis of their adrenal origin can have survived to the present day, as, for example, in MacCallium's text book [1942]. This hypothesis based on no more than a very superficial resemblance of parts of renal tumours to adrenal cortical tissue, should have become permanently obsolete in 1908 when Stoerk's complete refutition of it appeared. But, like many other already exploded hypotheses at has suffered all advised revivals in spite of repeated exposure of its falisty by Zohbe, Glynn, Ipsen, Wright, Nicholson, Derrick, Inglis and Jones and many others

I do not propose to enumerate the many objections to the Grawitz hypothesis, the falsity of which I think should be sufficiently clear from the structure of the tumours alone. Those interested in further details of the controversy—one which has claimed far more attention than it merits—will find all they need in the papers just eited. My own opinion is well expressed in Nicholson's words. For me the controversy was settled by Stoerk, and finally buried by Glynn, and the suprarenal origin of the hypernephromata disproved. To which I would add that I find it incomprehensible that any serious student of the subject, or indeed even an unbiassed beginner properly examining a few typical specimens of renal carcinomis and adenomas, could reach any other conclusion. Carrying as it does such objectionable implications, the name 'hypernephroma' should be discarded.

(5) Metastases

Renal careinomas are very fickle and unpredictable in their behaviour Some grow for long periods and to huge sizes without yielding metastases, others remain small and symptomless, yet produce large remote metastases usually by the blood stream. Metastatic growths have caused many errors of diagnosis (Willis, 1934. Trinca and Willis), and these growths sometimes appear in unusual situations, such as the skin muscles tonsil, oral or nasal mucosa larynx iris fingers etc. Following nephrectomy metastatic growths may soon appear in the lungs, bones or elsewhere or they may not appear until 6 8 or 10 years later, as in cases reported by Clairmont Albrecht. Fischer and Broster

hydraemic nephritis Some carcinomas are predominantly of solid celled type usually however with some clear celled areas



Fig 215 -From a metastasis in the myocardium in the same case as Fig 214 (x 120)

(c) Anaplastic variants spindle celled or pleomorphic celled and often diffuse and sarcoma like in appearance, have led to many erroneous diagnoses of



Fig. 216—Solid-celled carcinoma oddematous stroma (\times 120) unusually discrete distribution of tubular structures in

streoma circino-sarcoma or mixed tumour of the kidney. The structural versatility of renal carcinoma, still insufficiently appreciated by many

Other sites of clinically obtrusive metastases include the skin or subcutaneous tissues (Halstead, McNathin and Dean, Smyth, Deuticke, Busser, Bungeler and

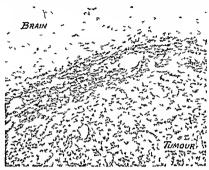


Fig. 217—A prominent zone of fibrin at the margin of a meiastasts of clear-celled carcinoma in the brain (× 40)

de Castro), the external auditory mentus (Benesi), the oral cavity (Coenen, Willis, 1931, Case 13, and see Figs 218 and 213 from case reported by Trinca and

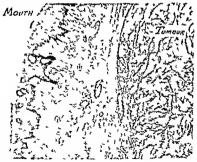


Fig. 218—Metastasis of clear-celled carcinoma in floor of mouth—from same case as Fig. 213 (see Trinca and Willis (1936) Case 14) (> 40)

Willis 1936) the laryan (Turner), the thyroid (Deuticke, Willis 1934, Case 188) the choroid or iris (Chance Kreibig Hudson and Lister)

Perhaps more often than any other tumour renal carcinomas produce solitary metastases in bone brain or other tissue (Albrecht, Scudder, Lehmann), and it has been claimed that surgical removal of both primary and secondary growths is sometimes curative in such cases (Smyth), a claim which it need scarcely be said, should not be made until there has been prolonged post operative freedom from recurrence

(a) Metastases in lymph glands

Deposits of growth are present in the lumbar lymph glands in about one half of necropsy cases. The glands regional to metastasis-containing organs also often contain growth especially the hilar glands when the lungs are affected Invasion of the thoracic duct occurs occasionally, e.g. in Winkler's Case 10 and Schwedenberg's Case 7

(b) Blood borne metastases

The frequency of metastass by the blood stream is explained by the proneness of renal cancer to invade vens, and examination of surgically removed kidneys for venous invasion is important in individual prognosis. The main sites of metastasis were exemplified in my series of 10 eases reported in 1941 in which metastases were present in the lungs in 8 cases (and in an additional case micro scopie intravascular tumour emboh were present), in the liver in 5, bones 4, opposite kidney 4, brain 3 thyroid 3, myocardium 2, adrenil 2 pancreas 1 and subcultaneous tissue 1 case. Metastatic tumours like primary ones often show a proclivity to invade main vens (Fig. 36)

The lungs contain metastases in at least three quarters of fatal cases and miliary metastases have been mistaken both clinically and radiographically for tubercles (Huguenin and Delarue). The her contains deposits in about one half of fatal cases. Trunca and I (Case XV) described a case in which exploratory operation for suspected gail bladder disease with jaundice revealed inva ion and occlusion of the common bite duct by a econdary growth.

The skeleton is a favourtie site of metastases which are present in nearly one half of necropsy cases. In my 1934 work I gave references to many cases in which metastases had simulated primary diseases of bone a subject specially discussed also by Rost, Gibson and Bloodgood Joli Deuticke and Lehmann Unusual sites of metastasis include the clavicle (Rost), metacarpais (Fabre and Dambrin) phalanges (de Massary and Weil) and jaws (Esau Stein Branch and Norton). The metastases are osteolytic and destructive often causing pathological fractures and often invading surrounding soft tissues. The tumours may show pulsation and may be mistaken for aneurysms (Eshner).

The brain contains metastases in about one quarter of fatal cases. Renal careinoma is third on the list of primary tumours most commonly responsible for secondary growths in the brain being exceeded in this respect only by careinomas of the breast and lung. Cirebril metastases may produce the main or only symptoms and so may cause misdiagnosis as in cases referred to in my 1934 work. A conspicuous zone of fibrin may develop around metastases of renal careinom in the brain (Neuburger and Singer and Fig. 217).

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√ (c) Retrograde venous metastasis ta the genitalia

This deserves special comment Tumour invasion of the spermatic or ovarian veins which of course is much more common from tumours of the left kidney than from those of the right may be followed by retrograde tumour embolism of the pampinform or ovarian plexus or the parametrial or vaginal veins, and the development of secondary growths in the spermatic cord epididymis parametrium, vagina of vulva Metastases of this kind in women have been described by Gellhorn, Hirsch Hoffmann, Fleischmann Gragert, and others and in men by Sutter and Derman In several cases the vaginal or vulval growths have been the first signs of disease Begg described a case in which priapsin due to secondary deposits in the erectile tissue was the main symptom of renal carcinoma

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tumours do not favour any special part, but in the wreter the lower part is the most often affected. For good accounts of the renal pelvic and ureteric growths, see the papers of Spiess. Meuker and McCarthy, Scholl (1924), Bissell, Siewart Rousselot and Lamon, D. Aunoy and Zoeller, Renner, and Kimball and Ferris.

The following is a noteworthy case of annular stenosing carcinoma of the

Case I—Male aged 60 Clinical diagnosis pyelonephritis Necropsy revealed a small annular stenosing growth at the junction of the middle and lower thirds of the right ureter. The pyonephrotic renal pelvis showed pronounced leucoplakia but the ureter near the growth was unaffected. No metastatic growths were found Histology—Diffusely infiltrating squamous-cell carendoma of the ureter advanced squamous metanlasia with much keratinization of the senal pelvis.



Fig. 219—Case II Carcinoma of preter A = closely packed narrow papillary structure B = more bulky epithelial masses with atypical areas (× 60)

J (4) Multiplicity

In a large proportion of cases the tumours are or become multiple, e.g. m 250 of the 902 cases of carcinoma of the bladder recorded by Kretschmer et al. Tumours of the renal pelvis are often accompanied or followed by tumours of the corresponding ureter or of the bladder, this association being the special subject of Kimball and Ferrirs 8 review. In 74 instances of this kind, the sites of the multiple tumours associated with main growths in the renal pelvis were the ureteric orifice and its immediate neighbourhood in 48 per cent of the cases the ureteric orifice and other parts of the bladder as well in 36 per cent, the bladder only in 14 per cent, and the ureter only in 2 per cent.

The following is an unusual example of simultaneous massive carcinoma of

the pelvis of the kidney and of the lower part of the ureter

CHAPTER 28

EPITHELIAL TUMOURS OF THE URINARY PASSAGES

ALTHOUGH regional grouping of the tumours of the urinary passages, namely of the renal pelvis ureter and bladder, is important to the clinician in diagnosis and treatment, it is of less interest to the pathologist for these passages are lined throughout by an identical transitional stratified epitbelium, the tumours of which in all situations show a similar range of structure and behaviour and almost certainly have a similar actiology. Further, although it is customary, and for clinical purposes useful to distinguish between benigh papillomas and carcinomas of the urinary tract epithelium it is impossible to make any real pathological distinction between them. Here more than in any other situation, there occur tumours showing every possible gradition and every possible sequence from solitary highly organized non invasive papilloma to disorderly invasive carcinoma. Any sub division of the whole group is necessarily arbitrary, and in this chapter therefore it is treated as a whole. Certain rare tumours of special origin—those of the tractus and of the urethra and its glands—are dealt with separately at the end of the chapter.

SEX AGE, SITE AND SPECIES INCIDENCE

(1) Sex

Men are affected more commonly than women in the ratio of about 3 to 1 in most series, as in the 902 cases of careinoma of the bladder in the registry of the American Urological Association (Kretschmer et al) and in the 74 cases of papillary growths of the renal pelvis collected by Kimball and Ferris My necropsies comprised 37 cases of vesical careinoma of which 27 were in men and 8 cases of renal pelvis and ureteric careinoma all but one of which were in men, giving a total of 34 men and 11 women.

(2) Age

The age distribution peak is early in the seventh decade. More than half of the cases occur between the ages of 50 and 70. The tumours are rare under 30 e.g. in only 5 of 902 cases of vesical cancer (Kretschmer et al.). The mean age at death of my 37 cases of carcinoma of the bladder was 64 and of my 8 cases of carcinoma of the renal pelvis or ureter 60.

(3) Site

The tumours occur in the bladder, renal pelvis and ureter in that order of frequency. This is probably related in a large measure at least merely to the relatite areas of mucous membrane in the three parts. In the bladder more than three quarters of the tumours arise on the lateral walls near the ureteric orifices or on the trigone or neck, while the posterior wall, fundus and anterior wall are the least frequent sites (Kretschmer et al). Tumours in diverticula are seen occasionally as in the case depicted by Scholl (1944). In the renal pelvis the

mucosa, and (d) the general analogy with multiple tumours in other epithelial organs, e.g. multiple polyposis in the colon, multiple papillomas in the mammary duets or multiple carenomas of the skin, in which multicentric origin is unequivocal. The arguments favouring urinogenous metastasis are (a) the "secondary' tumours usually appear, not fortuitously in any other part of the urinary tract but in relation to the initial tumour, e.g. in the corresponding ureter or bladder in eases of growth in the renal pelvis, (b) intervening parts of the mucosa may appear quite healthy and devoid of any signs of a pre cancerous state such as might suggest a general instability of the whole urinary tract epithelium, and (c) there is evidence that even extra urinary tumours may occasionally implant themselves within the urinary passages (see Böger's case cited in Chapter 10). The weight of the evidence seems to me to point to multicentire origin as being a much more important factor than urinary metastrasis.

(5) Urinary tract tumours in animals

Feldman (1932, Chapters XVII-XIX) and Nieberle and Cohrs (1931, p. 535) mention examples of papillomas and careinomas of the bladder in horses, eattle and dogs. Schlotthauer recorded two examples of squamous cell careinoma of the bladder and Stalker and Schlotthauer an example of squamous cell careinoma of the female urethri, in dogs. Langham et al. described multiple mucus secreting papillary adenomas of the bladder in cows.

POSSIBLE FACTORS IN CAUSATION

(1) And the tumours' of the bladder

The only clear instance of an occupational incidence of urinary tract tumours is in workers with aniline dyes. Attention was first called to this in 1895 by Rehn who recorded several cases of vesical cancer in fuchsine workers. A symposium by Ferguson, Gay and others in 1934 reviewed knowledge of the subject, while Hueper's paper (1938) and Chapter V of his book (1942) give admirable accounts of more recent clinical and experimental work. Thanks to the latter, the carcino genic properties of β naphthylamine have been proved, and there seems little doubt that this substance is the main, though perhaps not the only, carcinogen responsible for aniline timours' of the bladder. Other aromatic amines deserve study in this respect, and it should also be recalled that some other compounds, e.g. several azo dyes and acetylaminofluorene, have selective carcino genic effects on the urinary tract. It is quite possible, as Davis urged that some of the many dyes ingested in confectionery cordials and foods, or absorbed from cosmetics, as well as those used in industry, are responsible for some of the urinary tract tumours in man

(2) Schistosomiasis and urinary tract tumours

The many reports of carcinoma of the bladder associated with bilharzial infection have all come from Egypt Valuable accounts include those of Ferguson and Dolbey and Mooro, and Hueper (1942) has given a useful review of the subject Caution is needed however, before assuming that the parasite is the essential cause in these cases Almost all the reported cases have been in

Case II—Female agod 64 Routuse medical examination disclosed a palpable right abdominal tumour. Operative removal of the enlarged right kidney and ureter was performed the latter distended in its lower part by a cylindrical mass of growth which was cut across during removal. Cystoscopic examination however showed that the ureteric growth did not project into the bladder. The perimer—The kidney was much enlarged and consisted of a thick shell of white growth around a ragged central cavity with no residual kidney tissue usable. The removed portion of ureter was 12 centimetres long its upper half was patent and contained no growth. Its lower half was occluded and distended by a cylindrical mass of growth 15 centimetres in diameter. Microscopy (Fig. 219) showed papillary carrynoma of typical tunnary tract type still fargely confined within the renal capsule and ureter but with mixasion of the wall at some places.



Fig 220 -Case III Papillary carcinoma of bladder (> 60)

The following case exemplifies multiple growths in the bladder

Case III—Male aged \$2 with dysuna for many months attributed to prostatomegaly. Accrepas showed the bladder to be distended by a shagey mass of growth 10 centimeters in diameter which however consisted of 8 separate pedunculated tumours with unaffected inter-ening mucous membrane. The attachments of most of the tumours were on the lateral walls above the trigone the ureteric orifices were not involved. There were no metastases. Histobey (Fig. 220)—Papillary carcinoma of typical urinary tract type with luttle or no invision of the musch coat.

Multiplicity of tumours in the urinary tract has been attributed by some workers to implantation metastasis and by others to multifocal tumour formation. While metastasis by implantation in the urinary passages must be admitted as possible and even as probable in some cases (see Chapter 10 and Willis 1934) it is clear that multifocal origin also often occurs. In favour of multifocal origin are. (a) the cystoscopic appearance of early multiple tumours in the bladder (b) the microscopic structure of early growths which often show clear signs of genesis from the stratified epithelium still in progress (c) the improbability of detached tumour particles in the urine successfully grafting themselves on intact

as in Case I above Probably only occasional tumours take origin from previously leucoplakic epithelium Squamous change in careinomas of the urinary passages is usually a metaplasia in the tumour tissue itself, and does not denote that the tumours have been preceded by metaplasia.

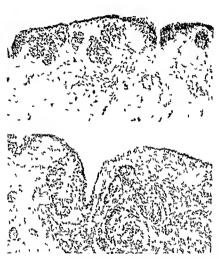


Fig. 221—Brunn's nests in chromic pyelitis. The largest nest in B shows early lumin formation (× 100)

(5) Other inflammatory diseases

Ewing's opinion that cystitis precedes careinoma in a high proportion of cases is not in accord with clinical experience. Surgeons with whom I have discussed the question are unanimous that in most cases of tumour the first symptoms of urinary disease are those caused by the tumour itself, and Kretschmer et all found no evidence of any pre-cancerous lesions in their large series of cases. There is no evidence that people with chronic obstruction of the urinary tract from strictures prostatic enlargement, tuberculosis or other causes are predisposed to cancer. Renal or vesical calcular found associated with tumours of the renal pelvis or bladder in about one quarter of the cases but it is clear that in most of these cases the calcular secondary to the tumours and of no causaive

Egyptians or Egyptian Atabs, amongst whom biliharzial disease is very prevalent, as much as 90 per cent of the population being infected in many districts. Hence it is inevitable that a high proportion of cases of utinary tract cancer in these people will be accompanied by the parasite even if no causative relationship exists between the two diseases. The evidence advanced that there is some causative relationship includes (a) estimates which appear to show that Egyptians with sehistosomiasis have a higher incidence of vesical cancer than Europeans and other non infested peoples, and (b) the occasional occurrence of vesical cancer in Europeans with chronic schistosomiasis, as in the case reported by Fauley As to (a), we must recall that estimates of the relative frequencies of particular diseases contain many potential fallacies, especially in hospital material which is often selected in various ways and that comparisons of the incidence of a given tumour in different countries especially when these differ widely in their standards of medical practice and registration are very hazardous (see Chapter 5) As to (b) cases of this kind are too few to warrant any deductions. In my opinion then, while it is quite possible that bilbarzial evstitis does indeed predispose to carcinoma the evidence is still not wholly conclusive and further eareful statistical and nathological investigation is needed

(3) Caremoma in exstrophy of the bladder

There is little doubt that exstrophy predisposes to carcinoma of the bladder McCown collected records of 25 cases of carcinoma of the exstrophed bladder, and Abeshouse also gave a useful review of the subject. Of the 27 timours reviewed 21 were adenocarcinomas, a proportion in striking contrast to that for carcinomas of the normally situated bladder, only 2 per cent of which are adenocarcinomas. As shown by Patch and Rhea and by Abeshouse cystic and glandular metaplasia is prominent in the exstrophied bladder, and it is the metaplastic epithelium which is predisposed to cancerous change. Carcinoma of the exstrophied bladder is most often situated in the upper part. It has the same sex incidence as vesical cancer in general, but may appear at rather earlier ages. Abeshouse s review comprised 17 men and 9 women of ages ranging from 23 to 66 years the greatest number (7) being in the fifth decade. Metastases have not been recorted.

(4) Metaplastic inflammations

(a) Cystitis pyclitis or ureteritis cystica and glandularis

This occurs not only in the exstrophied bladder but also in the normally situated organs as first described in 1893 by Brunn and later by Stoerk Stow Wilson Patch and Rhea and Abeshouse. All stages in the formation of Brunn's nests, in yests and mucus secreting glands can be traced and there seems no doubt that these changes predispose to adenocaremoma. The precise factors responsible for metaplasia of this type are still unknown. Fig. 221 depicts Brunn's nests in a hydronephrotic kidney of a man of 52 years, the whole pelvic mucosa was similarly affected.

(b) Leucoplakia

Leucoplakia of the urinary passages is seen in association with chronic tuber culous or calculous disease or with carcinoma, in a small proportion of cases

confined within the walls of the pelvis, ureter or bladder before invasion of surrounding tissues supervenes

(c) Cornifying squamous cell carcinoma (Fig 225)

This is a frequent structural variant in part or whole of many invasive tumours. Not uncommonly the superficial parts of a tumour consist mainly of papillary growth of type (b), while its deeper invasive parts are epidermoid



Fig 223 -Villous papillary carcinoma of bladder showing cellular pleomorphism (× 80)

(d) Anaplastic invasive carcinonia

This includes spheroidal celled, diffuse pleomorphic celled (Jolly) and a hacmorrhagic type resembling chorion epithelionia (Venulet) There is little doubt that many supposed 'sarcomas' of the bladder have been of this kind

Again it must be insisted that these are not distinct kinds of growth all gradations are seen and several or all of the structural variants may occur in one tumour

(e) Mucoid adenocarcinoma

This type well reviewed by Abeshouse constitutes about 2 per cent of carcinomas of the bladder. It arises chiefly in the trigone appears to be related to the condition of cystiits glandularis already referred to and often shows areas of transitional stratified structure as well. It is to be distinguished from mucoid urachil carcinoma (see below) which arises at the apex of the bladder and is said to be purely glandular in structure. Most carcinomas of the exstrophied bladder are adenocarcinomas. Govin described a benign mucus secreting cystadenoma of the bladder.

significance The rare condition of malakoplakia seen in some cases of chronic cystitis, well described by McDonald and Sewell and Chisholm and Tudhope apparently does not predispose to tumour The suggestion of Kirwin that urinary papillomas may be due to a virus is purely speculative

STRUCTURE AND GROWTH

Of the gross oppearances of the tumours which are plentifully illustrated in many papers and text books I propose to say little Gay's brief description of the aniline tumours" applies equally well to those of undetermined causation

The tumors are single or multiple papillary or sessile infiltrating or noninfiltrating ulcerating or non-ulcerating or there may be any combination or sequence of these characteristics.



Fig 222 -Well differentiated viltous papilloma of bladder (> 120)

(1) Microscopic structure

The following types of structure are found

(a) Highly organized villous papillars growth (F g 222)

This consists of a uniform layer of typical transitional stratified epithelium closely resembling that of the normal urinary tract clothing delicate viscular connective tissue papillice. This is the structure of the typical benign papilloma.

(b) Less highly organi ed papillary growth (Figs 219 220 223 224)

This shows epithelium still of urinars tract type but more bulky less regular including solid masses with little or no papillary arrangement and showing many mitotic figures. This is the structure of most papillary careinomas. Invasive properties may be much or little in evidence—many of the tumours long remain

recurrences are apt to assume mereasingly dangurous characters and to terminate eventually in invasive growth and metastasis. This sequence has been well described by Kretschmer et al., who found that in 38 per cent of cases with multiple vesical tumours, there was a history extending over a period of 5 years or longer in one case for 49 years, with repeated recurrence often terminating in frank carcinoma. They described the history of a typical case of this kind terminating in metastasis 13 years after initial removal of a "benign tumour

The disease apparently originates in multiple foci in the bladder mucosa appears first microscopically benign and may continue to appear so on repeated bionsy for years. From time to time new tumors will be found and if accurately it can be definitely shown that there is no recurrence in previously treated areas and that the new tumors represent true new growths and not In spite of the apparent benignity of the tumor under the microscope, the disease may infiltrate the lymphatics and metastasize or infiltrate nearby structures. The entire course of events may be spread over a period of Some multiple tumors are clinically malignant, no from 5 to 20 years matter how benign the tissue may appear under the microscope'

From the point of view of their behaviour and prognosis, urinary tract tumours

might conveniently be grouped into the following 3 groups

(i) Solitary tumours of 'benign" structure, some of these are cured by local removal others are the forerunners of multiple recurrent growths

(a) Recurrent multiple growths of" benign" structure comprise the dangerous group just discussed though of long duration the disease is not perma nently cured by local removal of individual tumours, and unless radical removal of the whole tumour bearing field can be carried out it will eventually terminate fatally

(iii) All other solitary or multiple growths of frankly cancerous or of atypical structure when first discovered, run a more rapid malignant course, and,

unless radically removable, end fatally in a few months or years

METASTASIS

Many papillary growths, even though structurally atypical in parts remain confined to the mucous membrane for long periods before they show invasive properties The metastasis of such tumours outside the urinary system is long delayed, so that, if operative removal is possible, such as nephrectomy for renal pelvic growths and if multiple tumours do not develop later in other parts of the urmary tract, cures are sometimes obtained. With invasive carcinoma, however metastasis to regional lymph glands or by the blood stream occurs early, as in cases of renal pelvic carcinoma described in my 1941 paper and cases of ureteric carcinoma reported by Jolly Invasion of veins, as depicted by McDonald and Priestley, is the prelude to haemic mutastasis

(a) Metastases in lymph glands

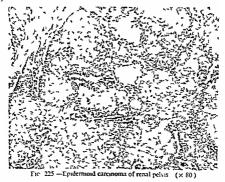
These are present in about one third of fatal cases, e g in 14 of my 45 necrop sies In my Case 217 enlarged glands in the neck were the first signs of disease and led to a false diagnosis of Hodgkin's disease, and in Case 228 the cisterna chyli and thoracic duct were cancerous

(2) Duration, change of structural type, prognosis

While some solitary papillomas are permanently cured by local removal the prognosis of any case of urinary tract tumour is uncertain. This is because



Fig 224—Pulmonary metastasis of the tumour of Fig 223 showing similarity of structure (× 80)



recurrence by multiple tumour formation occurs in a considerable proportion of cases initially regarded as benign and because with the lapse of time repeated

CARCINOMA OF THE MALE URETHRA

This is a rare disease In 1925 Diehl reviewed 61, and in 1939 Kreutzmann and Colloff 148, reported cases Of these 148 cases, 56 were in the filth decade, the age range being 18 to 91 years There was a history of stricture—gonorrhoeal or traumatic—in three quarters of the cases The site of the tumours is in the builbo membranous slightly more frequently than in the penile part of the urethra, and rarely in the prostatic part

(1) Structure and growth

In the great majority of cases the tumours are cornifying squamous cell carcinomas, and only occasionally papillary growths of transitional urinary tract type or adenocarcinomas, the latter doubtless arising from Cowper's or Littre's glands Deming and Lindskog saw an unusual case in which, over a period of 13 years multiple recurrent papillary growths of the hladder were followed by similar multiple tumours of the urethra Usually urethral carcinoma appears as a single growth, which, however, may widely invade the penis, scrotum or rectum and may cause priapism by invasion of the erecule usesue (Ikeda et al.)

(2) Metastasis

Metastasis takes place to the iliac, pelvic and inguinal lymph glands, which, however, are often found enlarged by inflammation while still free from growth Metastasis by the blood stream to the lungs, liver, or rarely to other parts may also occur

CARCINOMA OF THE FEMALE URETHRA

Vulval or vaginal growths not infrequently involve the urethra, but carcinoma of the urethral canal itself is rare. Shaw Culver and Forster, and Kaufmann give references to reported examples. Both squamous cell carcinoma of the surface epithelium and adenocarcinoma of the urethral glands occur. Caruncles are benign non neoplastic inflammatory lesions, which rarely, if ever, undergo cancerous change but they often show atypical areas of proliferating epithelium which can easily be mistaken for carcinoma by the inexperienced

EPITHELIAL TUMOURS OF THE URACHUS

The urachus, the remnant of the aliantois extending from the apex of the bladder to the umbilicus is not as is often supposed a simple fibrous cord but nearly always contains residual epithelial cords or small cysts Begg (1930) made a careful study of these residues, which consist of an irregular form of transitional stratified epithelium, which however, as age advances often gives rise to gland like outgrowths. Carcinomas or benign cystic growths may arise from these residues the former usually having the structure of mucoid papillary adenocarcinoma (Nuboer, 1925, Begg 1936 Willis, 1941 Case 383) Distinction of urachal carcinoma from mucoid adenocarcinoma of the bladder itself may

(b) Blood borne metastases

These are present in at least one third of fatal cases, e.g. in 16 of my 45 necropsies the organs most frequently affected being the bones lungs and liver Metastases in bones, as described by Kretschmer Joll Nicholls Graves and Militzer, are of special frequency and importance. Their distribution in the skeleton is that of metastatic growths generally, their most frequent sites being the vertebrae, ribs, pelvis femur and humerus, but they occur also in the skull, clavicle tibia radius, etc. The changes in the bones are usually osteolytic. Direct non metastatic invasion of the vertebrae or pelvis from the primary growths or their lymph nodal metastases also occurs as in Jolly s cases. The metastases in bones may show a highly differentiated papillary structure as in Nicholls's case in which also the affected bones showed osteoplastic changes.

While blood borne metastases from urmary tract carcinomas usually do not appear until relatively late stages of the disease exceptions to this rule are not unusual. As Kreischmer noted, metastases in bones particularly may develop early from quite small operable primary growths. The following cases exemplify widespread metastasis from small unsuspected primary tumours.

Case IV—Male aged 45 History—Increasing anaemia and weakness for some months with palpable enlargement of the liver. Disseminated malignant disease was suspected but no primary growth could be discovered. Necropys disclosed an area of infiltrating growth 15 centimetres in diameter at the apec of one of the pyramids of the upper part of the left kidney without gross ukeration into the pelvis and without any visible invasion of renal veins. There were large deposits of growth in many lumbar lymph glands many metastases in the liver extensive diffuse cancerous permeation of the pulmonary lymphatics and alveoli and widespread metastaic deposits in many bones especially the vertebrae and ribs. Microacopically the tumour was an anaplastic spheroidal cell careinoma but with areas showing recognizable, differentiation both of urnary transitional and squamous cell type. The rib metastases showed much new bone formation by the expanded personsterm.

Case V - Male aged 64 a diabetic History - Pain in the back and right leg commenced in October 1938 and was diagnosed as sciatica In April 1939 a large mass involving the right illum was noticed and skiagrams suggested extensive metastatic growth Necrops in the same month showed many secondary tumours in the lungs liver and vertebrae a large growth 18 centimetres in diameter replacing the right thum with much formation of new bone by expanded persosteum (Fig 25) a thyroid adenoma 2 centimetres in diameter containing a crescentic area of soft white growth 1 centimetre in main extent and a flat area 2 centimetres in diameter of papillary growth replacing the mucosa on the anterior wall of the bladder The tentative necropsy diagnosis was probable malignant adenomy of thyroid with widespread metastases Histology-The bladder tumour was a papillary carcinoma of typical transitional type slightly infiltrating the muscle coal. The tumours in the lungs liver bones and thyroid were clearly metastases of the vesical tumour, showing in parts distinct differentiation of transitional stratified characters with also some comification. The metastasis in the thyroid lay within an old fibrous partly calcified adenoma

In my other necropsies I have seen metastases also in the myocardium brain, thyroid kidney and adrenal. It is possible that urinary tract tumours may have a special tendency to metastasize in the heart cardiac metastases were present in 5 of Fergusons 40 cases of bilhararil cancer of the bladder and keynes saw a single nodule in the heart as the only metastasis of a renal pelvic carcinoma.

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not always be possible. The following is an example of a benign umbilical tumour probably of urachal origin

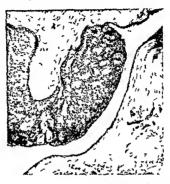


Fig. 226 -- Case VI Umbilical tumour probably of urachal origin. (x 60)

Case VI -For some years a woman of 38 had noticed a small mass beneath the skin at the border of the navel. This had enlarged recently and was excised. It was a well circumscribed loculated cystic mass 2.5 centimetres in diameter partly filled by friable papillars growth. Microscopically this consisted of thick folded layers of stratified epithelium devoid of spinous cells and comification generally resembling the urmary transitional epithelium and traversed by fine connective tissue strands with blood vessels (Fig 226)

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from vestigial or heterotopic tissues should not be admitted until it is certain that the normal tissues of the organ are incapable of producing such tumours, and (ii) 'embryonic rests' 'should not be invoked to avoid difficulties. Application of principle (i) will make us sceptical regarding the alleged Wolffian origin of serous cystadenomas, the alleged teratomatous origin of pseudomucinous cyst adenomas, the alleged mesonephric origin of certain papillary growths, and a too facile identification of 'hypernephroma' of the ovary while application of principle (ii) will engender caution in interpreting Meyer's views on the origin of several of the special ovarian tumours from superfluous groups of "undiffer entitled cells"

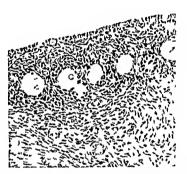


Fig. 227.—Ovarian cortex of an adult Australian phalanger Trichosurus sulpecula showing ova the cellular cortical blastema (stroma) and the germinal epithelium on the surface (× 250)

(3) Distinction of ovarian from parovarian or tubal growths

This is not always possible. When a large tumour has involved both ovary and tube, and perhaps many other pelvic structures as well, its primary site may only be surmised, and for statistical or classificational purposes it is best excluded it is noteworthy that the parovarium though a frequent source of cysts, very rarely gives origin to tumours, Nicholson (1923) recorded one example

(4) The mistaking of secondary for primary growths

This is a frequent error Bulky secondary growths in the ovary from small or silent growths elsewhere often simulate primary ovarian tumours and have caused many errors of diagnosis. The Krukenberg tumour now known to be always secondary usually to carcinoma of the stomach was regarded by Krukenberg as a primary ovarian growth. The ovarian metastases of silent alimentary

CHAPTER 29

EPITHELIAL AND RELATED TUMOURS OF THE OVARY

OVARIAN tumours show great structural variety, the histogenesis of some of them is clear while of others it is still obscure. Several factors have combined to cause confusion in their classification and nomenclature namely (1) uncertainties as to the histogenetic relationships of some of the tissues of the normal ovary, (2) uncertainties as to the derivation of particular tumours from particular ovarian insuses (3) practical difficulties in some cases of distinguishing growths of ovarian origin from those of parovarian or tubal origin and (4) the frequent mistaking of secondary for primary growths in the ovaries. It will clarify subsequent description if these several sources of confusion are first discussed.

INTRODUCTORY REMARKS ON CLASSIFICATION

(1) The histogenesis of the tissues of the normal ovary

There is sufficient evidence both embryological and pathological for discarding the older view of Waldever that the followiar epithelium is derived from down growths from the germinal' epithelium on the surface and is therefore sharply distinct histogenetically from the surrounding ovarian stroma. It now appears clear that the so called stroma' of the cortex of the ovary is not a mere sup porting tissue but an undifferentiated blastema from which both the epithelium of the follicles and the non enithelial thecal tissue arise. Examination of the primary follieles in young mammalian ovaries (Fig. 227) shows clearly that there is no structural distinction between those peri ovular cells which will give rise to the stratum granulosum of the maturing folliele and those which will give rise to its theea interna, both of these arise by divergent differentiation from the indifferent blastema cells surrounding the ovum. The cortical stroma is thus not a mere connective tissue it is the essential ovarian parenchyma and is distinct from the ordinary fibroblastic and vascular framework of the ovary Further in the young active ovary, the so called 'germinal epithelium on the surface is not everywhere sharply distinct from the subjacent cellular blastema, and it is probable that this epithelium also like that of the follicles is a product of, and closely allied to the labile subjacent cells Unjustifiably sharp distinctions between germinal surface epithelium granulosa-cell epithelium and thecal tissues have come from too close a preoccupation with these several end products of differentiation. The essential tissue of the functional ovary is its peculiar cellular stroma this is the plastic mother tissue from which the differentiated constituents of the organ are being constantly produced. This formative tissue then is sure to be of prime importance in the histogenesis of tumours

(2) The histogenesis of particular tumours

Here two important principles pertinent for any region but especially so for the ovary need emphasis—(i) derivation of any tumour or class of tumours of the normal adult ovary, of which the tumours appear to be but a neoplastic exaggeration. Papilliferous serous cysts of the ovary are clearly the same kind of growth, the cysts often having demonstrably arisen, as Shaw found, from the deeper parts of the surface crypts of the ovary. The once prevalent view that the intra ovarian papillary cystic growths were of Wolffian origin (see Ley) is certainly false, and it is noteworthy that, while cystic tumours of the ovaries are frequently papilliferous, parovarian cysts are very rarely so. The epithelium of the serous cysts and papillary growths closely resembles that of the surface of the ovary, and the fibrous connective tissue component corresponds

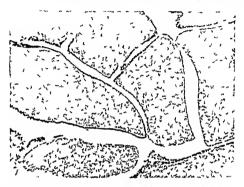


Fig. 228 —From an intracystic fibro papillary growth 15 centimetres in diameter in a woman of 64 (\times 60)

to the cortical ovarian stroma (Fig 228) The tumours are mixed timours, analogous to the mammary fibro adenomas, which they also resemble in showing varying relative proportions of epithelial and stromal tissues Some timours show predominance of epithelium and are appropriately called papillomas. Others show great masses of fibrous tissue clothed only on the outer surfaces by an epithelial layer these have often been called 'fibromas However, all possible transitions between and combinations of, fibroma, papilloma, and papillary and simple serous cystadenoma occur, and the whole series clearly constitutes a single group

The epithelium clothing the papillae varies from low cuboidal or flattened to tall columnar cells, and the latter sometimes show cilia and sometimes evidence of mucous secretion (Fig 229). The fibromatous component in actively growing tumours is cellular and resembles cortical ovarian stroma, but in old, less active tumours it becomes densely fibrous and partly hyaline. Granular calcification is often present. As pointed out by Lepper a property common to these tumours is the secretion of serous fluid by the epithelium, the fluid accumulating

and other abdominal carcinomas may show glandular, papillary or cystic structure distinguishable with difficulty or not at all from primary ovarian carcinomas. and may easily be mistaken for such by the pathologist as well as by the clinician unless the mistake is corrected by careful necropsy. As shown by the many references which I have given elsewhere (1934 Chapters 12 and 23), mistakes of this kind have certainly caused great confusion in clinical and pathological My necropsy experience accords with that of records of ovarian cancer Ley (1920) and others that secondary carcinoma in the ovary is commoner than primary carcinoma

The foregoing sources of confusion not only render all mortality statistics regarding ovarian cancer' valueless but also vitiate attempted analysis of the properties of ovarian tumours from many clinical series of cases as well. The mortality figures of ovarian tumours even were they based on accurate diagnoses. would still be useless for assessing the frequencies and properties of these tumours would still be users for assessing the relatively benign and are cured by surgery.

The only valid data for fruitful analysis are series of proved cases of specific kinds of turnours which have been identified by competent microscopical examination an identification which in not a few cases can be regarded as fully verified only after careful necropsy

We will discuss ovarian tumours under the following headings

(1) Benign fibro papillary growths and serous cystadenomas (ii) Pseudomucinous cystadenomas

(iii) Malignant growths-carcinomas-corresponding to or arising from (i) and (ii)

(iv) Brenner tumours

(v) Granulosa theca and luteal tumours

(vi) Arrhenoblastomas' (vii) Dysgerminomas

(viii) Sundry other tumours

This grouping is adopted for convenience and to include the currently accepted turnour types it is not intended to be taken as a rigid classification into distinct species or to denote acceptance of the implications of all the names used. My own opinion regarding histogenesis is stated under each heading and is summarized at the end of the chapter and I recommend a paper by Robinson (1930) for sound views on this subject. Geist's book (1942) contains useful figures and references

BENIGN FIBRO PAPILLARY GROWTHS AND SEROUS CYSTADENOMAS

(1) Incidence and causation

These are the commonest of ovarian tumours Small surface or intra-cystic growths are often discovered incidentally at operation or necropsy. They occur in adult ovaries of all ages are most frequent between 40 and 60 and may occur in old age. Nothing is known of their causation

(2) Structure and origin

The structure of the warty or cauliflower like growths which spring from the surface of the ovary is essentially similar to that of the corrugations and crypts

been required over a period of many years. I recall a patient who had been tapped over 200 times, and Bland-Sutton recorded a patient on whom 299 tappings were performed in 10 years. Spontaneous retrogression of disseminated peritonial growths sometimes takes place, a subject well reviewed by Taylor and Alsop.

SIMPLE AND PAPILLARY PSEUDOMUCINOUS CYSTADENOMAS

(1) Incidence and causation

Pseudomucinous tumours are second only to the serous ones in frequency. They are unusual under the age of 30 most of them develop between 30 and 50, and they are rare again in old age. Nothing is known of their causation.

(2) Structure and origin

These tumours are too well known to require detailed description. Their usual multilocular structure, with large or small cysts within cysts, honeycomb areas, their mucinous contents varying in consistency from slightly slimy fluid to inspissated firm jelly or stringy tenacious material, to which old or recent haemorrhages or cholesterol deposits may add still greater variety, their lining of columnar mucus secreting epithelium from which may spring papillary or convoluted intra-cystic growths their thick outer cyst walls, and the huge sizes they may attain, are all familiar features.

Although most cystadenomas of the ovary fall readily either into this group or the previous serous group, some tumours are of borderline characters Thus a unilocular cyst with all the appearances of a serous cystadenoma may yet contain slightly mucinous contents, or a multilocular tumour may show serous contents in some of the cavities and mucinous contents in others. These transitional types of cystadenoma are of significance in considering the origin of the pseudcmucinous tumour Three different opinions regarding this have been held (a) that it represents overgrowth of a single component, usually considered to be alimentary, of a teratoma (b) that it is related to the Brenner tumour (see belon), and (c) that it is related to the serous cystadenoma mucus secretion being acquired by metaplasia in the epithelium I favour the third view, which however, does not exclude the second The first view I regard as wholly speculative and devoid of any substantial basis If it were true, we would surely see frequent examples of pseudomucinous tumours along with other obvious teratomatous tissues, but this is not the case. The occasional coexistence of teratoma and pseudomucinous tumour, of which I have myself studied examples, is too rare to be more than fortuitous on careful search, the vast number of pseudomucinous tumours show no signs of teratomatous elements Morcover, the alimentary and other mucus secreting epithelia in teratomas do not resemble pseudomucinous cyst adenomatous tissue, they are usually accompanied by muscle coats and often by lymphoid tissue, so that typical intestinal structure is reproduced And does not ovarian pseudomucin differ chemically from alimentary or respiratory mucin? The fact that the pseudomucinous epithelium is unlike any normal component of the ovary is no argument for its teratomatous origin, metaplasia in tumours is frequent and no one suggests that mucoid carcinoma of the breast is teratomatous in origin. The rather frequent occurrence of tumours which

within the cystic growths or producing ascites from the surface ones. Scott has given a good account of a special sub group of the beingn serous epithelial tumours which he has designated adeno fibromas, in which small glandular spaces are scattered through solid fibromatous tissue. These growths often show granular calcification and papillary characters in parts and they clearly represent only a particular type of the papillary exists serous tumours.

The mode of origin of the tumours is of interest. Many of them clearly arise



Fig. 229 —From pedanculated papiliary growth in a unifocular ovarian cyst containing slightly mucinous watery fluid in a woman of 70 $(\times 60)$

over extensive fields of the ovarian surface and papillary tumours are often found springing simultaneously from the surface of the ovary and from the interior of one or several cysts in the ovary. Bilateral growths are frequent, and these are due to similar neoplastic change affecting both organs simultaneously or successively and not to metastasis from one to the other.

(3) Growth and behaviour

The tumours of this group grow slowly and non invasively producing symptoms only by their bulk or by causing assets of this kind may yet disseminate in the peritoneum without showing any alteration of structure the implant tumours showing the same beingin appearance and non invasive growth as the parent tumours. When this happens we must concede the appropriateness of now colling them careinomas yet they have not really altered in their characters. These growths thus show, like many others that no shirty demarcation between innocence and malignancy is possible. Peritoneal dissemination of course increases the fluid output of the growths and every gynaecologist is familiar with cases of this kind in which frequent tappings have

with (a) and (b) in the more malignant tumours, or may form the bulk of them (Fig 230)

(d) Squamous cell structure, due to metaplasia, has occasionally been found in cystadenocarcinomas, as in cases described by Nicholson and Rewell

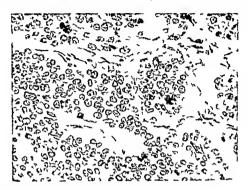


Fig. 230 —From an hepatic metastasis of a solid spheroidal-celled careinoma of the ovary note mitotic figures (× 300)

(3) Growth and behaviour

The tumours frequently become bilateral, grow to great sizes fill the pelvis, invade neighbouring viscera, eause intestinal obstruction or spread to the anterior bildominal wall. Peritoneal dissemination is frequent, leading to ascites, glatinous accumulations widespread adhesions, or combinations of these. Transdiaphrag matte extension to the pleura and mediastinum is not unusual, and may cause the first signs of disease, as in Evans and Straehans ease. In surgical treatment of operable malignant ovarian tumours, Pemberton advised removal of the omentum as well as the uterus and both tubes and ovaries. Sampson's work leaves no doubt that frigments of ovarian carcinoma can implant themselves in the mueosa of the Fallopian tubes.

(a) Metastases in lymph glands

These are present in a high proportion of fatal cases, e.g. in 12 of my 17 necropsies. Ley recorded a decided difference between milignant pseudomucinous tumours and solid or papillary non mucinous tumours in this respect, no lymph nodal deposits were found in any of 9 cases of the former, while in the latter 12 of 16 cases showed affected lymph glands. The thorace duet is occasionally affected. In a case described by Gibson and Findlay, the first symptom of disease was a large mass in the neck, presumably in lymph glands from which

combine mucinous and serous characters seem to me to point to their common origin from the ovarian epithelium. Careful study in serial sections of some very small pseudomucinous cysts is needed.

(3) Growth and behaviour

In their slow non invasive growth to large sizes, in the formation in some tumours of masses of papillomas, and in their usually favourable prognosis, pseudomucinous tumours resemble their serous counterparts. They differ from them in uncomplicated cases in not forming papillomas on the surface of the ovary and therefore in not causing secretory asertes. Rupture of the eyst walls by trauma or by the growth of prolific intra eystic papillomas however, leads to spilling of quantities of the mucinous secretion and of mucus secretory cells into the perstoneal cavity and to "pseudomyxoma perstonea" (See the original paper of Werth (1884) and other references by Willis, 1934)

OVARIAN CARCINOMAS OF SEROUS OR PSEUDOMUCINOUS ALLIANCE

(1) Age incidence and causation

The mean age at death of my 17 necropsy cases of ovarian carcinoma was 59, and the youngest patient was 32. In Pemberton's clinical series of 149 cases the mean age was 49, 46 and 47 cases were in the fifth and sixth decades respectively i.e. a total of 61 per cent in the two decades, and the youngst patient was 26. I have seen a multilocular papillary cystadenocarcinoma, 20 centimetres in main diameter removed from a girl of 14. Pemberton s cases showed no significant poculiarities of menstrual history or fertility.

(2) Structure and origin

No sharp line of demarcation can be drawn between the more active papilliferous cystadenomas on the one hand and the invasive papillary cystic or solid cartinomas of the ovary on the other. All gradations of structure and behaviour are seen justifying the designation cystadenocarcinoma which has often been applied to such tumours. The development of invasive cancerous growth in part of an elsewhere benign serous or mucinous tumours is sometimes demonstrable. The carcinomas corresponding to or arising in the cystadenomas constitute the majority of malignant tumours of the ovary or the ovarian cancers of mortality stitustics.

The varieties of structure seen in these careinomas include the following

(a) Papillary adenocarcinoma resembling or identical with the more active papillary growths in the cystodenomas or showing varying degrees of anaplasia is found in most ovarian carcinomas. Some of the papillary tumours of serous cystadenomatous origin show characteristic granular calcification—so called psammo-critinomas. (see Fig. 43)

(b) Cistic nucoul adenocarcinoma usually with papillary characters as well is a common type of growth and is the malignant variant of pseudomucinous cystadenoma

(c) Solid spheroidal celled or diffuse pleomorphic celled growth is found mingled

cells first described by Walthard in 1903. These cell nests, which appear as small well defined yellowish nodules or tiny cysts on the surface of the ovary, tube or broad ligament, and which have not infrequently been mistaken for /tubercles at operation, have a microscopic structure closely similar to that of the solid and cystic clumps of the Brenner tumours (Fig. 231). Danforth drew attention to a peculiarity of the nuclei common to the cells of Brenner tumour and of Walthard nests, namely a distinctive median fold or groove giving the nucleus the appearance of a wheat grain



Fig 231 -A Walthard nest on the peritoneal surface of the Fallopian tube (× 120)

The resemblance of Brenner tumours to the Walthard nests is indeed so close that it seems presumptuous to express any doubts regarding the now widely accepted origin of the one from the other But it is necessary to point out that, while Walthard nests are more common in the serous coat of the tubes or broad ligament than in the ovaries, no extra ovarian Brenner tumours have been reported Moreover, unreserved acceptance of the Walthard nests as the origin of Brenner tumours raises fresh difficulties as to the origin of the cystadenomas, since there seems to be no doubt (1) that Brenner tumours are related histogenetically to pseudomucinous tumours (ii) that pseudomucinous and serous cystadenomas are not sharply separable, and (iii) that serous cystadenomas and fibro papillomas arise from the surface epithelium of the ovary However, the great diversity of structure in the cell groups found in or near the ovaries affords an explanation of these relationships These include nests of granulosa like cells or of columnar, ciliated or goblet cells, or of stratified squamous like epithelium like that of the Brenner tumours, and they serve to show the variety of structural differentiation of which the gonadal and juxta gonadal tissues are capable. If this is recognized, then tumours showing combinations of cystadenomatous and Brenner structure will cease to surprise us and we will be prepared to readmit Brenner's original view that tumours of this kind may arise also from the ovarian follicles

the tumours had invaded the subclavian vein and superior vena eava and projected into the right atrium

(b) Blood borne metastases

These are relatively infrequent, they were present in only 4 of my 17 necropsies. The lungs and liver are the usual sites but other viscera and bones are affected occasionally (Bankart Erdhem) Nieholson (1909) saw multiple pulmonary netastases from a well differentiated pseudomucinous growth

BRENNER TUMOURS

(1) Incidence

In 1907 Brenner described 3 cases of the tumour which now bears his name in believed it to arise from the epithelium of the follules and accordingly named to oophoroma folliculare. In 1932, Meyer recorded 22 cases and distinguished the tumour sharply from the granulosa cell tumour. In 1935 62 cases had been reported (Bland and Goldstein). In 1939, 122 cases (Novak and Jones), and in 1942. 170 cases (Fox)

The age distribution of the tumours in successive decades was shown by Fox s review to be as follows

| Decade | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | Total |
|-------------------|---|---|----|----|----|----|----|---|-------|
| Number of cases - | 0 | 1 | 11 | 26 | 41 | 47 | 27 | 5 | 158 |

The tumours have been bilateral in 8 per cent of the cases, 3 of Fox s 4 cases had bilateral tumours

(2) Structure and origin

(a) Gross appearance

Huge tumours of 18 and 15 pounds have been seen but most tumours are of small or moderate size. They may be wholly solid or may show a solid mass of growth in the wall of a cyst usually a pseudomucinous cystadenoma as in the cases of Hieks and of Marwil and Beaver. The tumour tissue is firm and fibrous in texture and often has a distinctly vellowish colour.

(b) Microscopic appearance

Well defined rounded nests or trabeculae of large polyhedral epithelial cells are set in a plentiful dense fibrous stroma. The nests may be solid or may contain small rounded well defined easities and the epithelium often appears stratified. The cells lining the small eystic spaces sometimes assume the typical form of columnar mucus secreting epithelium and in different cases, all transitions between typical Brenner epithelial nests and pseudomucinous cystadenomatous structure are seen.

(c) Origin

Brenner's suggestion that his tumour arose from the epithelium of the ovarian follieles has been widely displaced by Meyer's view that it arises from nests of

luteal cells, it is equally certain that granulosa cells also become luteal cells Case III below showed very clearly the lutenization of groups of granulosa cells In view of the origin of granulosa cellshelm from undifferentiated ovarian stroma, it is not surprising that lutenization may affect either of these and the controversy as to whether luteal cells come mainly from "epithelial" or "non-epithelial" precursors loses interest

"non-epithelial" precursors foses interest

This view of the relationships and maturational changes in this series of tumours is now adopted by most informed writers on the subject, e.g. Traut and Butterworth Harvey et al. and Bettinger et al. Other noteworthy contributions include Loffler and Priesel's account of 6 theca cell tumours showing transitions from plump lipoid rich cells to fibrous tissue, Novak and Longs outline of ovarian tumours with hormonal effects, and Furth and Butterworths study of granulosa cell and other tumours in the ovaries of irradiated mice. Under the apt heading Life Cycle of Graafian follicle like Tumors, Traut and Marchetti pointed out the wide variation in degree of maturation in the different parts of granulosa cell and theca cell tumours "The result of periodic growth is that the neoplasm is frequently an aggregate of groups of cell masses produced at different times and having different degrees of maturity and senescence." The hormonal effects of the tumours vary according to the total amount of functionally active tissue at any given time.

(2) Age incidence, site, causation

A few oestrogenic tumours have occurred in young people, even before puberty Probably the youngest subject with a tumour of this type was Southam's patient of 2 years and 10 months in whom vaginal bleeding, enlarged breasts and the growth of pubic hair were relieved by removal of an ovarian tumour said to be a round celled sareoma' Bland and Goldstein reported a granulosa cell tumour in a child of 7 with precocious menstruation, which was relieved by removal of the tumour but later recurred when a second tumour developed in the opposite ovary However, only about 10 per cent of granulosa cell tumours appear under the age of 20, and about 50 per cent of them appear after the menopause Theca cell tumours are rather later to appear than granulosa cell tumours only about 10 per cent of these appear before the menopause.

Predominantly granulosa cell tumours – 10 39, 46 56, 66

Predominantly theca cell tumours - - 57 72

Tumour with granulosa and theca cells in nearly

Granulosa cell tumours are bilateral in only a small proportion, about 10 per cent of cases. The cacell tumours are rarely bilateral. Extra ovarian granulosa cell or the cacell tumours have been described in the broad ligament e.g. by Ragins and Frankel and by Powell and Black and I have examined one specimen of this kind given to me by Dr. H. Bettinger, a typical granulosa cell tumour of trabecular pattern weighing 800 grammes, from a woman aged 56 (Fig. 232)

Nothing is known of the causation of these tumours, but Furth and Butter worth s experimental production of them in mice by means of X rays is of great

interest

(3) Growth and behaviour

Brenner tumours grow slowly are well circumscribed and are eured by surgical removal Recurrence and metastasis have not been reported, and there is no evidence that any of the carcinomas of the ovary are malignant virtuants of the Brenner tumour. However, slightly sugmented growth and slight anaplasia might readily disguise a tumour of Brenner type and lead to its inclusion amongst the solid or cystic carcinomas of the ovary, without more specific recognition Brenner tumours are usually unaccompanied by hormonal disturbances, but in Marwil and Beaver's case a structurally typical Brenner tumour was associated with endometrial hyperplasia and haemorrhage in a woman of 77 Bettinger reported the coexistence of uterine carcinoma and myomas with a Brenner tumour and a pseudomucinous cyst.

GRANULOSA CELL. THECA CELL AND LUTEAL TUMOURS

(1) Introductory

The term granulosa cell tumour was originally applied to various solid epithelial tumours solely on micro structural grounds e.g. by Werdt (1914) Lepper et al. (1932), and many others. But as it became recognized that some of these growths produced oestrogenic hormone, it became customary to restrict the name to tumours accompanied by signs of hyperoestriusm. This restriction of the term however, introduced two difficulties on the one hand there occurred tumours structurally of granulosa cell type, yet without obvious hormonal effects, and on the other hand there were some tumours with such effects but of non-epithelial structure.

The first difficulty is not a serious one, in all groups of endocrine tumours we encounter some usually the less well differentiated members of the class, which are without demonstrable endocrine effects. We shall then admit as granulosa cell tumours any which are structurally characteristic even though they

are devoid of functional results

The second difficulty, that of distinguishing between granulosa-cell and theca cell tumours is resolved by recognizing the histogenetic relationship between granulosa and theca cells in the ovary as outlined at the opening of this chapter Just as the granulosa and theca cells of the ovarian follieles are products of divergent differentiation of a common mother tissue, the undifferentiated ovarian blastema so granulosy-cell and theca-cell tumour tissue are closely akin and are indeed often present tog ther in a single tumour (Traut and Marchetti, Dockerty, Henderson) All the tumours of this group are fundamentally tumours of the formative ovarian stroma epithelial and thecal differentiation in them proceeding in varying proportions and to varying degrees. Moreover the tumour tissue undergoes maturation changes comparable with those of normal follicles namely luternization and band like librosis and hyaline change. Luteal-o'll tumours are thus allied to or but variants of granulosa-cell and theca-cell tumours, and no doubt dense fibromas of the ovary are the end product of tumours of this series just as the corpus fibrosum is the end product of the ovarian follicle. The cell transitions observed in the tumours are of interest as regards the still debated origin of leuteal cells-whether from the granulosa epithelium or from the thecal stroma While it appears certain that stroma cells can differentiate directly into

Epithelial granulosa cell structure—Some growths show a well differentiated folliculoid pattern, at once recalling that of the normal stratum granulosum and showing Call Exner bodies or conspicuous rosettes (Figs 233, 234), it was this type which von kahlden originally described in 1895 as "Grasfian follicle

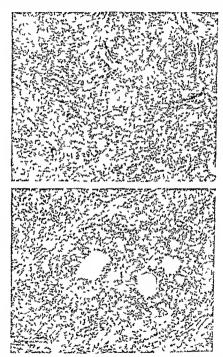


Fig. 233—From a granulosa-cell tumour of the ovary in a woman of 66 showing many Call Exper rosettes and small cysts. (x 100)

adenoma ' Or the epithelium, though still composed of typic il granulosa cells, may form irregular trabeculae or coarse or fine networks (Fig. 235), or the

(3) Structure

(a) Gross appearance

Granulosa cell tumours are well circumscribed usually stoutly encapsulated growths, consisting of firm white or patchily yellow solid tissue which, however, may contrin small or large cystic spaces Hormonal results lead to the removal of some of the tumours while still small, but in many other cases the growths

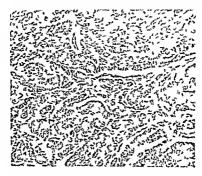


Fig. 232 - From a huge granulosa-celt tumour of the broad ligament in a woman of 56 (x 120)

have attained large sizes. The specimen removed from a Nigerian woman by Kelsey weighing 20 pounds, is probably the largest recorded. Most theca cell tumours are wholly solid, consisting of firm fasciculated tissue resembling fibrous tissue but often with a distinct yellow colour. However some of these growths contain cysts—and one of my specimens—a large tumour from a woman of 57 consisted of a single cavity surrounded by a wall of tumour tissue measuring up to 3 centimetres thick.

(b) Microscopic structure

This is well described and depicted by the writers already cited and is shown also in Figs 232-238. It is important to recognize that epithelial and stromal tissues often coexist in one tumour that one tumour may show great diversity of structure from part to part and that all gradations may be seen between the several types of structure. However most tumours do consist predominantly of one or another type of tissue so that the names 'granulosa-cell tumour, there-cell tumour and luteal-cell tumour have descriptive value.

ovarian stroma, or they may be indistinguishable from fibrocytes, forming interlacing fasciculi with plentiful intercellular collagen fibres. In the more cellular areas the cells usually contain plentiful doubly refracting lipoid droplets which stain characteristically with fat stains. Lipoid rich parts of the tumours have a distinct yellow colour on section. In the more fibrous areas intra-cellular lipoid material is more scanty. Cellular and fibrous areas may alternate, and banded fibrous and hyaline zones may recall the appearance of corpora fibrosa at different stages (Fig. 236). There is no doubt that many, if not all, fibromas of the overly are really fibrous these cell tumours.

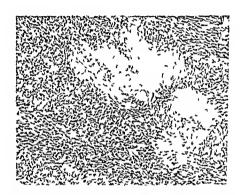


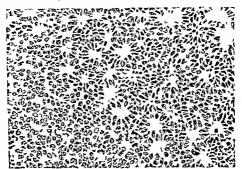
Fig. 236—From a theca-cell tumour 10 centimetres in diameter from a woman of 22 (Case II of Buttinger et al.), showing fibrous patches like corpora albicantia in the cellular growth (× 120)

Luteal cell structure —This is frequent in parts of granulosa cell or theca-cell tumours and is sometimes predominant, giving the tumour a bright yellow colour like a giant corpus luteum (Henderson) Geist et al and Traut et al have given useful accounts of lutemization in these tumours

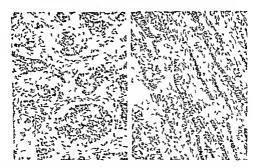
(4) Origin

In the preceding discussion it has been implied that the granulosa and theea cell tumours arise from the normal follucular tissues or from the formative bipotential ovarian stroma. There is no need to suppose with Meyer and with Novak [1941] that these growths are "embryonic" or "dysontogenetic" and that they cannot arise from normal ovarian structures. Furth and Butterworth's experiments

epithelial cells may be scattered rather diffusely amidst accompanying undifferentiated stroma (Fig. 238)



Fir 234 -Detail of the rosettes of Fig 233 (x 300)



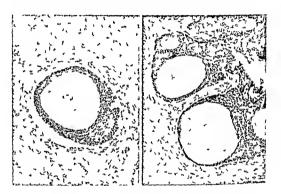
f ic 235 —From a granulosa-cell tumour 10 centimetres in diameter weighing 400 grammes from a woman of 46 (> 100)

There cell structure —This shows spindle cells arranged in groups or bundles. The cells may be plump and closely packed resembling those of undifferentiated

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solid and partly cystic with a thick fibrous capsule. The other ovary appeared normal After removal of the tumour the uterine haemorrhages ceased. Histology—Small and large cystic spaces were lined by irregular thick layers of epithelium of granulosi-cell type and solid areas consisted of masses and trabeculae of similar epithelium containing small cysts (Fig. 237). There was much intervening stroma consisting of poorly cellular soft fibrous tissue.

Case II—A married woman aged 39 had had amenorfnoes for 3 years followed by recent return of menstruation and had noticed a lower abdominal tumour for some months. At operation a large right ovarian tumour without adhesions was removed the left ovary and uterus appeared normal. The tumour was smoothly ovoid with a thick fibrous capsule and weighed 900 grammes. On section its tissue was pink grey finely spongy with many tiny and some larger cystic spaces. Histology—Typical granuloss cell tumour mainly of trabecular and folloculoid structure with eviste spaces.



Fic 237 -Case 1 Cystic granulosa cell clumps (> 80)

Case III - A married woman aged 52 mother of 3 children the eldest 25 and the youngest 18 gave the following unusual menstrual history Menses commenced when she was 18 years old occurred regularly every 4 or 5 weeks but were copious and lasted 10 to 14 days During the previous 12 months they had occurred every 6 or 7 weeks but lasted about the same time as previously For 3 months abdominal enlargement had been noticed and examination showed uterine prolapse and signs of a large ovarian turnour This was removed along with the enlarged uterus The turnour comprised a large cyst containing clear serous fluid and with a slightly granular or papillary liming and at one side a well defined mass of solid growth 3.5 centimetres thick with a fibrous cut surface and a distinct yellow colour The endometrium measured up to 1 centimetre Histology (Fig 238)—The solid part of the growth consisted of mingled cellular and fibrous stromal tissue with however many scattered patches of well differentiated granulosa cells including many luteal cells The latter were clearly luteinized granulosa cells all transitions from the one to the other were seen. All transitions were seen also between cellular stroma and epithelial cells. The turnour was thus an excellent example of mixed stroma-cell granulosa cell and luteal-cell structure

afforded good evidence that granulosa cell tumours in mice do indeed arise from the granulosa epithelium of the ovarian follicles and that this tissue is not, as has often been asserted a satellite tissue entirely dependent for its existence on the presence of ovar Proliferation of follicular epithelial and interfollicular spindle shaped cells both of which are probably derivations of the germinal epithelium give rise to granulosa cell tumors. These tumors may be composed of spindle shaped cells like those of the ovarian stroma or of epithelial cells like those of ovarian follicles or of luternized epithelial cells, or of several different morphological variants of the granulosa cells. In brief in accordance with the principle enunciated earlier in this chapter we can interpret the structure and relationships of the tissues in these tumours in terms of the normal structure and functions of ovarian tissue, without resort to hypothetical origins from rests or superfluous groups of undifferentiated cells.

of superfluous groups of undifferentiated cells. Probably however, granulosa cell tests—are not exempt from neoplasia, extra ovarian granulosa cell tumours may arise from such heterotopic cell groups.

(5) Endocrine effects

As described in the papers of King and of Meyer Novak and Long Trait and Marchetti and others, the most characteristic endocrine result of functional granulosa cell and theca cell tumours is cystic endometrial hyperplasia sometimes as in the case described by Arnold et al, with decidual change in the hyperplastic endometrium. Occurring before puberty, precocious sexual development and menstruation are induced, occurring in adults before the menophuse the result is either menorrhaga or amenorrhoca followed by irregular beleding occurring after the menophasis irregular severe uterine haemorrhage results. Many of Furth and Butterworth's muce with granulosa cell tumours showed endometrial hyperplasia. Mammary enlargement and secretion have been recorded in a few cases.

Uterine abnormalities other than endometrial overgrowth have frequently been noted in association with these ovariant tumours. Ang s cases showed /multiple myomas and adenomyosis. Of Henderson's 21 cases of granulois-cell tumour. 5 had uterine fibroids and 2 had careinoma of the endometrium while of 9 cases with theea-cell tumours, 5 had fibroids and 3 had endometrial careinoma. Thus of the total 30 cases. 10 had fibroids and 5 had earcinoma—proportions too great to be fortuitous suggesting that the prolonged oestrinization was indeed a factor in causing the uterine tumours. Stohr reported 3 cases of well differentiated follieuloid granulosa-cell tumours with accompanying endometrial hyperplasia and supervening earcinoma. Furth and Butterworth sin an excessive number of mammary tumours in their mice with experimentally produced ovarian tumours. A fruitful research would be to study the follow up history of all eases of granulosa-cell and theea-cell (and other) tumours of the ovaries for possible subsequent lesions of the uterus or breasts (see Case IV below). Whether luteinized ovarian growths produce excessive progestin has not yet been determined.

The following 4 of my eases were noteworthy because of their hormonal disturbances

(6) Mahgnancy and metastasis

With few exceptions, tumours of both granulosa-cell and theea cell types are relatively benign, in most series recurrence or metastasis has been infrequent. Novak and Brawner, however, reported chinical malignancy, either extension to peritoneum or recurrence, in 9 of 36 cases of granulosa cell tumour, and Traut and Marchetti found climical or histological evidence of malignancy in 8 of 54 tumours studied. But it must be recognized that disorderly or diffuse structure in these growths does not imply clinical malignancy and that a false histological diagnosis of malignancy may easily be made. In Henderson's series of 30 cases, only 1 granulosa cell tumour recurred, and none of his 9 thecomas was malignant. In none of my 8 cases was recurrence or metastasis reported.



Fig. 239—Case IV. Cystic endometrial hyperplasia accompanying theca-cell tumour in a woman of 72. (< 4)

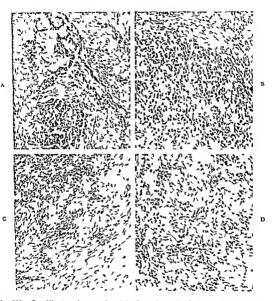
In the remarkable case described by Arnold et al, the patient died of recur rent growth at the age of 63 20 years after removal of the primary ovarian tumour, and metastases were present in the peritoneum, liver, vertebrae, ribs and many lymph glands

TUMOURS ACCOMPANIED BY MASCULINIZATION ARRHENOBLASTOMAS

(1) Introduction

The name arrhenoblastoma" was applied by Meyer in 1930 to rare ovarian tumours accompanied by signs of masculinization, including amenorrhora sterility atrophy of the breasts and uterus enlargement of the clitoris, and

Case IV (Dr. F. G. C. de Crespigny s. case)—A married woman aged 72 complained of irregular uterine hacmorrhage for the last 8 years. Radical removal of the left breast for carcinoma had been performed 7 years ago. Operation revealed a large right ovarian tumour which was removed along with the enlarged uterus. The tumour was mainly



in 238—Care III A = clumps and tendrils of granulosa-cells B = partially jutenized area of granulosa cells C = the ca-cell structure D = trabecular hyaline fibrosis in a threa-cell area of the growth (ν 100)

solid but partly cystic and measured 20 centimetres in diameter. The uterus showed great thickening of both the endometrium and myometrium. Intrology—Predominantly theca-cell tumour with alternating areas of poorly cellular fibrous tissue and undifferentiated cellular spindk-celled stroma, but containing also groups of polyhedral epithelium like cells. The endometrium measured up to 1.5 centimetres thick and showed extreme cystic hyperplasa (Fig. 239).

structures closely like those of granulosa cell tumours Mechler and Black reported a case and reviewed other records of "gynandroblastomas", 1e tumours accompanied by masculinization but with continuation of menstrial bleeding and other signs of hyper oestimism. Microscopically these tumours have shown no constant structural pattern, they have been regarded as combinations of granulosa cell tumour and arrhenoblastoma", and lipoid laden cells in them, as in the arrhenoblastomas", have been regarded as I eydig cells



Fig. 240—Case VI Arrhenoblastoma A shows slight and B pronounced luteal change in the epithelial masses (× 100)

Some tumours have contained glandular structures lined by columnar mucous enithelial cells

Kanter and Klawans described masculmization in a woman of 33, with a huge cystic ovarian tumour evidently of teratomatous nature, containing

hairness. Although it has often been assumed largely because of the name, that these tumours must arise from testicular elements in the ovary, this is doubtful and their precise histogenesis is uncertain (see below). The best reviews are those of Buttner (1932) and Noris (1938). Most of the tumours have appeared before the menopause—the age extremes of the few reported cases are 16 and 66. They are almost always unilateral. Nothing is known of their causation.

(2) Structure

There is nothing distinctive about the gross appearance of the tumours. They may be large or small wholly solid or partly cystic white or yellow

Microscopically also, the structure is usually non distinctive and variable Some of the growths have consisted wholly or in part of tubular glandular tissue Meyer and others say that this resembles that of Pick's 'adenoma tubulare' of the atrophic cryptorchid testis, the structure of which is similar to that of tubular adenomas of the ovary unaccompanied by hormonal disturbanees (Heesch). But most 'arthenoblastomas' show no microscopical characters sufficiently distinctive to relate them to any special structures consisting of solid carcinoma-like cpithelial trabeculae and masses with or without suggistions of glandular structure or of diffuse growth devoid of recognizable cpithelial characters or of all of these. Bottuch depicted regimented cell groups Mucoid' glandular actin have been described in several tumours. I have studied two specimens of 'arthenoblastoma'.

Cate V (Dr. C. S. Fit_patrick s case)—A married woman of 32 complained of sterility Het mentes had been normal until 31 years earlier when complete amenorrhoea developed This was unrelieved by intensive oestrin treatment. Distinct features of masculinization included hypertrophy of the clitoris and strophy of the breasts. Laparotiony disclosed a small well defined rounded tumour 2 centimeters in diameter in the right ovary which was removed. On section the tumour consisted of greysh pink solid tissue. Microscopically thus showed well-defined anastomorius good epithelial cords with some tiny cystic spaces but no definitely glandular lumina. The structure closely resembled that of the trabecular variety of granulosts-cell fumour

Case I (reported by Dr. II. & McInture. 1942)—A solid yellowish right sided ovarian tumour was removed from a woman of 26 who had developed marked hairness and an enlarged chtoris. Histology (Fig. 240)—The tumour was a mixture of epithelial cords and diffusely cellular tissue. The cords consisted m unity of closely packed small polyhedral cells, with however many groups of larger vacuolated cells like from cells resembling the luteraized cells of granulosa-cell tumours. Between the epithelial trabeculae lay diffusely cellular growth consisting of polyhedral and irregular cells otherwise resembling those of the trabeculae. At one part of the periphery lay an area of uniform syndle-celled growth drowd characters and structurally resembling thea-cell tumour.

(3) Nature and origin

In both of the foregoing cases, the microscopic resemblance of the tumours of organulosa-cell tumours and the presence in one of them of both theca-cell like truncell like structures raise the question of the possible relationship of these tumours to those of the Graafian folliele group. In other reported cases also the tumour structure and the hormonal effects have raised the same question. Thus in Mackenrodt's case No. 14 (tabulated by Büttner) the tumour was recorded as granulosa-cell like in parts and Benecke depicted follieuloid.

Yet many permanent eures have been obtained by removal of the tumours in the early stages. In Norris's case a small primary tumour produced widespread metastases in the liver, lunes, mediastinum, kidney, adrenal and opposite ovary

SEMINOMA LIKE TUMOUR OF THE OVARY 'DYSGLRMINOMA

The name dysgerminom was applied by Meyer to solid carcinomatous ovarian tumours with a microscopic structure resembling that of seminoma of the testis and devoid of endocrine effects. Indeed French pathologists had previously called these tumours ovarian "seminomas" and had supposed them to arise from testicular elements in the hilum of the ovary. Meyer, however, assumed their origin (and also the origin of seminomas of the testis) to be from undifferentiated germinal cells of indeterminate type. Werdt's case VI, classified by him as a granulosa cell tumour, was clearly one of dysgerminoma. The best reviews of the subject are those of Scegar and of Sailer which cover over 100 cases.

(1) Age, site, causation

(a) Age

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About three quarters of the subjects are under 30 years of age, and about one half of them under 20. Young children however, are not affected, the youngest recorded ease being 9 years old

(b) Site

The right ovary is more often affected than the left Seegar's review showed right sided growths in 48 per cent, left sided in 26, and bilateral growths in 26 per cent of eases and Sailer's 5 cases had 4 right sided tumours and 1 left sided Following removal of a unilateral tumour, the risk of development of a second tumour in the remaining ovary is slight, this has been recorded only occasionally, e.g. by Potter In 6 recorded cases, following removal of one affected ovary the patient has had a subsequent fruitful pregnancy

(c) Hermaphroditism or pseudo hermophroditism

This has been present in a singularly high proportion of eases. Meyer's original review comprised 27 tumours associated with and 21 without pseudo hermaphroditism, and he stressed that dysgerminoma is the commonest tumour of the gonads in pseudo hermaphrodites. The frequency of the association was probably over estimated by Meyer, because the interest excited by it led to its being frequently recorded, the proportion of subsequently reported cases of dysgerminoma with associated pseudo hermaphroditism has been much lower Dysgerminoma in pseudo hermaphrodites accurs at rather later ages than in other subjects—pseudo hermaphrodites have provided a large proportion of the tumours over the age of 30. A positive Aschieim Zondek or Friedman test has been observed in a few patients with dysgerminoma (Potter)

(2) Structure and origin

The tumours are usually well defined completely solid composed of firm homogeneous white tissue, degenerative or cystic changes are usually not prominent. Large sizes have often been attained before operative removal, in

in addition to embryonic rete and 'arrhenoblastoma' tissue, glandular cysts and cartilage (How could embryonic rete and 'arrhenoblastoma' tissue be identified in a teratoma ") Mcchler and Black also suggested that "gynandroblastomas' may be teratomatous. To add to the confusion regarding the nature and origin of masculinizing tumours of the ovary we must also admit the possibility of adrenal cortical tumours occurring in this organ since accessory rodule of adrenal cortex are sometimes present in the peritoneal tissues near the ovary (see below). The tumour described by Jolles and Gleave (1945) as arrhenoblastoma in an hermaphrodite woman of 61 has no claim to that title there was no evidence that it had androgenie activity

In an important paper Burrows (1943) warns that it is a gross mistake to suppose that because a tumour produces androgen it therefore should have an architecture like that of the testicle. In the male, androgens are derived from the interstitial glandular cells of the testicle which have no tubular or strand like arrangement' The structure of arrhenoblastomas' is unlike that of inter stitual cell tumours of the testis Again, 'Some ovarian tumours which induce hirsuties and other masculine phenomena are the colour of corpora lutea and are composed of cells which resemble those of luteal tissue others might be described from their cytological appearance as thecomas or as granulosa cell tumours and yet others look like tumours derived from adrenal tissue. In fact by examining sections of an ovarian tumour under the microscope no reliable guidance can be obtained either from their anatomical arrangement or individual appearance as to the nature of the hormones if any which the cells may have Burrows concludes 'Criticism is made of the terms arrheno blastoma and granulosa cell tumour and it is suggested that they might be discarded It is proposed that the term arrhenoma might be used to denote androgen producing tumours and theeloma to denote those which produce oestrogen arrespective of the location of the tumours in the body or of their histological appearance '

I agree with Burrows that the name ' arrhenoblastoma has conveved a false implication of origin from male gonadal tissue and that the androgen producing tumours of the ovary to which it is applied are of undetermined and possibly of diverse nature. But I think the terms—granulosa-cell and theca cell tumour—can legitimately be used to designate tumours which elearly correspond to these elements or their precursors in the normal ovary, and which often though of course not always produce the appropriate hormone—The histogenesis of the oestrinizing tumours is I think well established—that of the androgen producing tumours is still uncertain—It would not be surprising if further research should show that the two classes of tumours are really one and are both derived from the ovarian prienchyma—Oestrogens and androgens are closely kindred substances—and are readily interconvertible both in the body and in utro (Burrows 1945)—Androgenie activity of an ovarian tumour may well be the result of dis 'turbed chemistry in a primarily oestrogene issue.

(4) Growth and metastasis

The androgen producing tumours of the ovary appear to be rather more malignant than the oestrogen producing granulosa-cell and theca-cell tumours

Patient remained well until April 1943 when she began to suffer from attacks of abdominal pain which were thought to be due to recurrent growth and which improved following deep X ray treatment. In April 1944 skiagrams showed large rounded shadows in the right lung field deep X ray tradiation was followed by marked diminution of these in October however right sided pleuril effusion had developed and multiple skellings had appeared on the chest and skull the largest 3 centimetres in diameter. X ray irradiation of these also led to their reduction. The patient died in December 1944 at the age of 22. Weeropsy showed many parily white and parily sellows and degenerated metastate growths in many abdominal thoracie and cervical lymph glinds in the lungs liver both adrenals subcutaneous tissues skull ribs and pelvic peritoneum. From the pelvic deposits the uterus was extensively invaded from the lumbar lymph nodal deposits the right kidney was invaded and from the massive thoracie lymph nodal deposits the growth had invaded the 6th and 7th dorsal victobrae in decompressed the spinal cord causing paraplegia.



Fig 241 -Case VIII Dysgerminoma from a metastasis in lung (x 120)

The left ovary was intact and rather small Histology—In all situations the tumours had a similar structure more cellular than that of the primary growth with less plentiful stroma and with many mitotic figures (Fig. 241)

SUNDRY OTHER TUMOURS

To conclude the list of epithelial tumours of the ovaries the following remain for consideration

(1) Epithelial tumours of teratomatous origin

Otherwise benign teratomas of the ovary occasionally give rise to squamous cell carcinoma argentaffin carcinoma or other growths of a single tissuecomponent. These are described in Chapter 61, where also the relationship of thyroid tumours (ovarian strumas;) to teratomas is discussed.

my two cases described below the tumours weighed 1,900 grammes and 3 350 grammes respectively

Seminoma like summarizes the microscopical appearances of the tumours which consist of well defined or ill defined groups or columns of large rounded epithelial cells set in a connective tissue framework of variable amount and density, accompanied by a variable number of lymphocytes (Fig. 241)

The histogenesis remains obscure. The favourite view is Meyer's that the tumours arise from ' indifferent germ cells' -whatever that may mean The early age incidence, the significantly frequent association with pseudo hermaphroditism, and the preference for the right ovary certainly suggest a relationship to some developmental disturbance. Whether the tumours are indeed seminomas derived from persistent male tissue in an indifferent bisexual gonad is uncertain but I think, not improbable. Against this view it has been argued that the dysgerminomas are more benign in behaviour than testicular seminomas but this argument is of little weight, for the growth of seminoma in the female might well progress very differently from seminoma in the male because of endocrine differences between the two sexes. It is noteworthy here that seminomas of the testis in dogs though clearly the counterparts of those in human beings are relatively benign. However, too much stress must not be placed on the close histological resemblance of dysgerminoma to testicular seminoma for other tumours also sometimes mimic seminoma in appearance e.g. some pineal and pituitary tumours (q v)

(3) Growth and metastasis

Though more tardy and less aggressive in growth than testicular seminomas and sometimes cured by surgical removal the seminoma like tumours of the ovary are essentially malignant and capable of metastasis. Maften referred to the recorded instances of metastases in lymph glands and peritoneum and described a case in which the first sign of disease was the appearance of a large lymph nodal metastasis in the neck. In Kirishbaum and Newman's case, necropsy 3 years after removal of the ovarian growth showed many deposits in the lunes liver kidness and peritoneum

The following two personally studied cases exemplify the two opposite termina tions of the disease—cure of a large tumour by excision and extensive dissemination. The second case also illustrates the radio sensitivity of the tumour.

Case 1 II — Ilistory — An otherwise healthy nurse aged 21 had noticed an abdominal miss for several weeks and laparotomy revealed a smooth surfaced irregularly cool often outrain immore which was easily removed. This weighed 1900 grammes measured 21 > 12 × 12 centimetres, and consisted of uniform firm white growth decoid of any pattern and without cysts. The patient remained in good health over 6 years later Ilistoly; — Large spheroidal-cell carcinoma of typical seminoma like appearance with masses and columns of large polyhedral cells s*t in a moderately abundant librous stroma containing a few hyphocytes.

Cate IIII—Illut m—In August 1940 a garl aged 18 had noticed abdominal discomfort and enlargement for 2 months and a diagnosis of fibroid was made Laparotomy however revealed a large sold irregularly oxold tumour of the right ovary which was removed. This weighed 3300 grammes (over 7 pounds) and consisted of uniform firm white growth without cysts. Histol en—Seminoma like growth generally resembling that of the previous case but with more himpheolies in the stroma. Subsequent progress—

serous cystadenoma, his Figures 15 and 20 strongly suggest ovarian parenchy matous tumours of the usual kinds, while in his Cases IX and X the "mesone phroma' itssue was a component of teratomas. The figures accompanying the description of Kazancigil et al of 3 cases of "papillo endothelioma' show clear epithelial structures and in their Case I they recorded that granulosa and follicle like structures were 'included in the tumour Stromme and Traut observed that the tumours sometimes contained mucus secreting or serous epithelium and granulosa or thecal elements. In the following case glomeruloid structures and micro cysts lined by flat epithelial cells with bulging nuclei like those of "mesone phromas", were striking features in a tumour in which a variety of other structural variants was present.

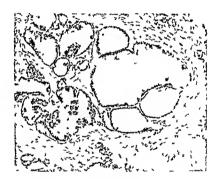


Fig 242 —Case IX Mesonephroma (× 60)

Case IX -A woman of 52 had recently noticed abdominal enlargement. At operation a right ovarian tumour was removed. This was 15 centimetres in diameter, had a fibrous outer capsule and consisted of a single large cavity with slightly turbid watery contents enclosed by a tumour wall measuring up to 2 centimetres thick from which nodules of growth projected into the cavity Histology (Figs 242 and 243)-The main cavity and many minute cysts in the solid growth were lined partly by flat epithelium with bulging nuclei and partly by cuboidal or low columnar epithelium these several variants being continuous with one another Papillary ingrowths were present in many of the spaces. glomeruloid structures were abundant Some papillary areas showed plentiful granular calcification others showed large clear cells and had a structure closely like that of renal carcinoma Solid epithelial nests were also present and some of these closely resembled Walthard or Brenner clumps In the solid part of the growth the epithehal cysts and nests were set in an abundant cellular stroma consisting of closely packed plump spindle shaped cells resembling those of thecomas This cellular stromal tissue showed transitions to the abundant, poorly cellular fibrous tissue which formed the main framework and capsule of the tumour

(2) Heterotopic adrenal cortical tumours

In an excellent paper in 1921 Glynn concluded that there was no acceptable report of the presence of accessory adrenal tussue in the ovary, that all so called ovarian hypernephromas were structurally unlike adrenal cortical tumours that they were also functionally unlike them in not producing the sexual changes seen with adrenal tumours and that they were probably all luteal cell tumours. These conclusions still hold, no proven ease of adrenal tumour of the ovary has yet been reported. None of the recent claims to have seen such tumours, e.g. those of Reis and Saphir is supported by adequate evidence. These growths are all lutenized ovarian tumours, and it must not be forgotten that lutenization may be seen in masculinizing growths as in Fig. 240

(3) Heterotopic renal tumours

Some writers, e.g. Saphir and Lackner, have described clear celled carcinomatous or hypermephroid tumours of the ovary, unaccompanied by masculinization which they suppose to be identical with renal carcinoma and to have arisen from renal elements included in the ovary. There is no evidence to support this assumption. Most 'hypernephroid' tumours are either luteal tumours or papillary cystic tumours with clear-celled areas (see Case IX below), while bulky metastases of renal carcinoma also occasionally occur in the ovaries and may simulate primary growths (Stadiem kannerstein et al.) Young and Lowrys diagnosis of 'renal blastocytoma of the parovarium in a woman of 45 is. I think, very doubtful

(4) Schiller s mesonephroma

In 1939 Schiller described eystic tumours in which he detected 'glomerula', glomerular like structures and abortive renal tubules', and which he supposed to have arisen from mesonephric tisse included in the ovary. While many subsequent writers accepted as a distinct entity the kind of tumour described by Schiller its mesonephric origin was disputed and several other equally specula tive opinions were advanced e.g. that it was a papillo endothelioma (Kazancigl et ol) or a 'teratori cystadenoma (Stromine and Traut)

From the literature of the subject (most of which is of a poor standard descriptively) and from my own examination of several specimens of supposed mesonephroma not only am I of the opinion that these views regarding its histogenesis are unfounded but I very much doubt if it is a distinct entity Schiller's glomeruli' and abortive renal tubules are highly imaginary similar structures can be found in many an adeno papillary growth not only of the ovary but of the prostate bowel thyroid or breast. The appearance of the low cells with bulging nuclei hing the small cysts in the tumours does not warrant sharp separation of these from other papillary growths. Once again as so often before in the history of oncology a mere habit of growth resulting in a superficial resemblance of tumout tissue to some normal structure has led to an unfounded and unnecessary assumption of origin from aberrant tissue.

It is noteworth, that several writers on mesonephromas have recorded the presence in these growths of structures relating them to other well known ovarian numours. Schiller's I igure 18 shows the typical intracystic papillary growth of a

Case XII—A Scotch collic aged 6 years had had a vaginal discharge for 6 weeks. An ovariant tumour and enlarged uterits were removed by operation pyometra was present in lower uterine segment and in upper end of one hom. Opposite ovary was replaced by tumour 10 centimetres in diameter consisting of areas of solid yellowsh growth between a honeycomb of cysts up to 2 centimetres in diameter with watery contents. Histology—Solid epithelial masses and epithelial sheets iming cystic spaces, consisting of large irregular polyhedral cells many of which are vacuolated. The appearance is that of a granulosa-cell growth with advanced laterization.

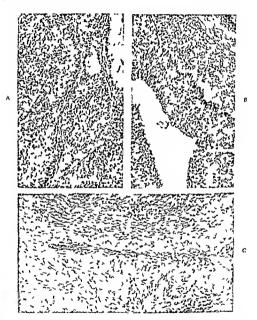


Fig. 245—Case AIII Ovarian tumour from a mare. A and B show granulosa-cell clumps and layers. C = folded hyaline bands like those of corpus albicans in a theca-cell area of the growth (x 120).

Case AIII —A racing mare 6 years old find had irregular oestrus for several years and more recent debihity and abdominal enlargement and was destroyed Necrops)—Abdominal early contained fluid right ovars was replaced.

This tumour was thus of great interest in showing not only the relationships of structures supposed to typify mesonephroma but also other structural variants showing an alhance with ordinary papillary cystadenoma with hypernephroid tumours with Brenner tumours and with theea cell tumours

SUMMARY OF PERSONAL CONCLUSIONS REGARDING THE HISTOGENESIS OF OVARIAN TUMOURS

He would be a bold man who in the present immature state of our knowledge, would dogmatize regarding the origins and interrelationships of the many and

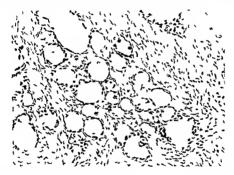


Fig. 243—Case /A Mesonephroma Note the small cysts. fined by flat cells vith bulging nuclei and abundant cellular stroma. (× 120)

diverse types of ovarian tumours. But the evidence discussed in this chapter appears to me to show plainly—(a) that with exceptions so rare as to be negligible all the kinds of tumours described arise from the gonadal tissues themselves and not from included heterotopic tissues and (b) that many or all of the several kinds of growths are interrelated and that various structural combinations are frequent. In my belief our views of this difficult field are clarified by assuming that the several differentiated components of the normal ovary—the follicular epithelium theeal tissue, luteal tissue corpus fibrosum and the germinal' epithelium—are all produced during adult life from the multipotent ovarian parenchyma or stroma that many of the tumours take origin not from an already differentiated particular derivative, but from this formative parenchyma and exhibit divergent differentiation and maturational changes like those of the normal ovary—not flat the diversity of structure seen in different tumours and often in one tumour arises from this divergent differentiation and maturation

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by huge cystic tumour weighing 20 pounds and consisting of multiple cysts up to 3 centimetres in diameter containing bloody fluid with intervening areas of white solid or finely cystic growth Histology (Fig 245)—Typical granulosa and theen-cell tumour consisting of large solid and cystic masses of granulosa epithelium with intervening undifferentiated cellular theca-cell tissue merging into fibrous tissue. In many places typical follicle like arrangement of granulosa epithelium theca interna and theca externa is seen. Hyaline bands like those of corpora fibrosa are plentiful in the stromal tissues

The 3 tumours from dogs are of interest not only because they show papillary and granulosa cell structures resembling those of human tumours but also because more than any human material they suggest kinship of these two kinds of growths. Further careful studies of canine and other animal ovari in tumours ire needed

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CHAPTER 30

CARCINOMA OF THE FALLOPIAN TUBE

INTRODUCTION

The pathology of tubal earcinomy has been confused by two prevalent errors, namely (a) the incorrect microscopical diagnosis of cyrcinoma in eases of tuberculous salpringitis, and (b) the incorrect diagnosis of secondary growths in the tubes as primary ones. These two sources of error make doubtful the correctness of the diagnosis in not a few reported cases, and partly viti its statistical and other generalizations regarding this discuse

As to (a), many writers on the subject, from von Franque (1911) to Novak (1941), have stressed that the epithelial proliferation necomp injung tubal tuber culosis may easily be mistaken for careinom. I myself have made this mistake on two occasions, diagnosing cocustent tuberculosis and careinom on sections which, reviewed in the light of further experience, I am now quite satisfied show tuberculosis only. When the tuberculous changes are plential and obvious these will serve to warn against a too hasty diagnosis of disorderly epithelial changes as cancerous. Sometimes however pronounced epithelial proliferation occurs with little or no microscopical evidence of tuberculosis in the same area, and an erroncous diagnosis of careinoma may be made even by an experienced pathologist. In such a ease, the absence of genuine cellular anaplasia and of distinct infiltration of the surrounding tube wall by the supposed growth should arouse suspicion and should lead to careful eserch of sections from other parts of the tube for signs of tuberculosis or of immistable experience.

As to (b), namely the confusion of primary with secondary carcinoma of the tube. Orthmann, who was the first to describe tubal carcinoma in 1888, was also the first to insist that secondary disease of the tube from primary ear-enomy of the ovary or uterus is frequent and may easily be mistaken for primary tubal carcinoma. In cases like the following in which papillary growth is present in both tube and ovary. I believe it is often impossible to determine the primary site with certainty

Case I—Surgically removed issues from a sterile matried woman of 69 years consisted of (a) right oray and tube the tube normal but the ovary represented by a smooth lobulated mass $6 \times 4 \times 3$ centimetres partly cystic and partly composed of masses of frable white growth (b) left ovary and tube the outer two thirds of the tube distended to a diameter of 3 centimetres by masses of white parpliary growth which also profused through the abdominal ostum and the ovary $10 \times 8 \times 6$ centimetres and like its fellow in structure (c) sex-tral large fragments of frable growth which lay free in the abdominal cavity. Microscopically all of the growths showed similar active adenocarcinoma of cystic papillary type (Fig 246) Sections of the broad ligaments ovarian pecifics and right tube showed no growth and ulterine curvitage some weeks later Lave simple endometrial tissue only 11 was not possible to decide whether the case was one of bilateral cystadenocarcinoma of the ovarines with a metastatic implant in the lube, or of primary tubal carcinoma with ovarian meristastes.

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| Ages - | ~ | - , | 25- | 1 30- | 35~ | 40- | 45- | 50~ | 55~ | Over 60 |
|------------|------|-----|-----|-------|-----|-----|-----|-----|-----|---------|
| Cases - | - | - | 3 | 6 | 23 | 41 | 44 | 32 | 22 | 6 |
| Percentage | ·s ~ | - 1 | | | 13 | 23 | 25 | 18 | 13 | |

Thus nearly one half of the patients were in the fifth decade, and two thirds of them were between 40 and 55 years of age The youngest was 27 years old



Fig 247 -Case II Papillary adenocarcinoma of the tube (× 105)

(3) Marital state, parity

Of the 196 patients reviewed by Wechsler, if miscarriages are disregarded, 47 (ie 32 per cent) had never borne children, 147 had been pregnant, and of these 43 had had only one child In many cases the last pregnancy had occurred many years before the development of the growth

RELATION TO SALPINGITIS

Doran Wechsler and others have believed that tubal carcinoma is often preceded by pelvic inflammatory disease. Some more recent writers, e.g. Ewing, endorse this view, while others, e.g. Novak, doubt it. The evidence for the former opinion, as outlined by Wechsler was as follows: (a) although a history of pelvic inflammation was seldom recorded in the cases reviewed by bird, his figures, cited above denoting a relative degree of sterility in the subjects of tubal carcinoma suggested that previous salpinguis had often been present; (b) the frequent association of tubal carcinoma with tubo ovarian cyst, and the

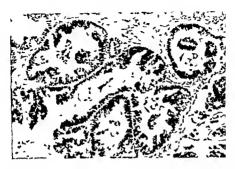


Fig. 246 -Case 1 Papillary adenocarcinoma of either tubal or ovarian origin (× 105)

It is probable that unrecognized primary growths other than ovarian or uterine may also produce confusing secondary disease of the tubes. I have seen a pair of surgically removed tubes both of which were evenly thickned and which the microscope unexpectedly showed to be diffusely infiltrated by signet ring-cell earcinoma. In another case, excised tubes diagnosed at operation as bilateral pyosalpinx, were found to be distended by large masses of solid growth which also infiltrated the tube walls and surrounding tissues microscopically this was a poorly differentiated spheroidal celled carcinoma, with nothing to suggest its origin. In such a case, while a provisional diagnosis of tubal carcinoma may be made, this diagnosis cannot be held to be certain unless subsequent, necropsy proves the absence of a primary growth elsewhere. Kaufmann saw massive distension of both tubes by mueoid carcinoma of gastric origin.

These then are the reasons for accepting only with reserve the following generalizations regarding careinoma of the Fallopian tube

INCIDENCE

(1) Frequency

Tubal careinoma is a rire disease accounting for less than 1 per cent of all female gential cancers (Martzloff). Orthmann who reported the disease for the first time in 1888 found 84 eases on record in 1906. In 1926 Weehsler found 196 reported cases, and by 1940. Martzloff found over 360.

(2) Age

Weehsler's review of 177 cases of specified age showed the following age distribution

In the meantime, an open mind must be preserved on the question as to whether tuberculosis of the tube, or other kinds of salpingitis may evoke neoplastic change in some cases. An answer to this question might well be attainable by a more thorough microscopic study of the tumours and of the other parts of both tubes in all cases of tubal carcinoma. Such a study might show that inconspicuous tuberculosis or other inflammation is more commonly present than is revealed by examination of only a few sections of the growth.

SITUATION AND STRUCTURE

Weehsler found that of 183 cases the tumours were right sided in 64, left-sided in 62, and bilateral in 57. Later writers also are agreed that the growths are bilateral in about one third of the eases. They usually occupy the outer or middle portions of the tube the uterine end of which is often unaffected, so that the enlarged organ is pear-shaped with its narrow stalk situated medially. That the outer parts of the tube are most often affected accords with the distribution of epithelium in the organ, the outer parts of which contain abundant folded mucosa while the mucosa of the inner third is relatively scanty. Many of the growths project from the fimbriated opening into the peritoneal cavity as friable papillary or cystic grape like masses. Not seldom the growth is related to a tubo ovarian cyst in which case it is often difficult to distinguish between tumours of tubal and ovarian origin.

The microscopic structure

Most tumours are distinctly papillary and cystic cavities with intra cystic papillary formations may be present as in Case II. Areas of solid epithelial growth may often be seen in parts. While parts of the best differentiated tumours may show an epithelial pattern closely resembling that of normal Fallopian mucosa the structure is never distinctive enough to permit confident microscopic distinction between tubal and ovarian papillary carcinoma. Designation of the best differentiated growth as adenomas or papillomas, as suggested by Doran by Bland Sutton and by other carlier writers is not justified. Papillomas should not be regarded as distinct from carcinomas but merely as the most highly differentiated, and therefore least malienant, members of the entire group.

SPREAD AND METASTASIS

The tumours soon reach the peritoneal cavity either by direct extension through the abdominal ostium or by invasion through the tube will Spread to the ovaries or pelvic peritoneum then occurs and widespread trans coelonic dissemination often ensues as in Case II Metastatic deposits in the pelvic or abdominal lymph glands are commonly present at operation or necropsy though it is likely that as with endometrial carcinoma lymph nodal metastaces are often absent as long as the growths are confined within the tube itself. Unfortunately this early stage of the disease is seldom seen by the surgeon who usually finds the tumours in an advanced inoperable stage. The prognosis in general is therefore bad and permanent cures are seldom obtained. The least unfavourable

not uncommon presence of hydrosalpinx of the opposite tube, also pointed to earlier inflammatory disease, and (c) all four of Wechsler s own cases showed evidence of such disease

While it is true as already noted that an incorrect diagnosis of tubal carcinoma has sometimes been made in cases of tuberculous salpingitis the coexistence of genuine carcinoma with tuberculosis has been reported by several writers, e.g. by von Franque by Callahan et al. (1929) and by myself (Willis 1934) My case was as follows



Fto 248 -Case II From a perstoneal metastasis (× 105)

Case II - History - For I year before her death a married woman aged 38 years suffered from abdominal enlargement and recurrent ascites which laparotomy showed to be due to tubal caremoma with extensive peritoneal metastases. Aecropsy showed large cystic distension of the right tube 12 centimetres in diameter, fined by masses of ragged papillary growth, which projected through the abdominal opening of the tube and also extended through its wall in several places. Widespread deposits of growth and adhesions were present in all parts of the peritoneal cavity and the spleen and liver were directly invaded from the deposits on their capsules. The inguinal iliae lumbar coeliae mediastinal and right and left cervical lymph glands contained large deposits of tumour and the eisterna chyli and thoracic duct were closely invested but apparently not invaded. There were no blood bome metastases in the viscera Histology -In all situations the tumours consisted of cellular adenocarcinoma with many mitoses showing papillary structure in many places (Figs 247 and 248) Sections of the less distended part of the tube towards its uterine end showed in addition to growth areas of typical easeating tuberculous tissue with many giant cells and Ziehl Neelsen's stain revealed many tuberck bacilli. No tuberculous tissue was found in any of the metastatic growths

Whether the coexistence of tubal earetnomy and tuberculosis is due to the former predisposing to the latter or vice versa or is purely fortuitious cannot be decided until a statistically significant number of proved cases has accumulated

CHAPTER 31

EPITHELIAL TUMOURS OF THE LITERUS

The Main subject of this chapter is uterine carcinoma. Some of the localized endometrial and cervical polypi are, no doubt, benigh tumours—papillomas or adenomas but it is difficult or impossible to separate these from the diverse forms of hyperplasia to which the uterine epithelia are liable. In a concluding section we will consider those rare uterine tumours in which both epithelial and non epithelial tissues participate.

SOME GENERAL ASPECTS OF UTERINE CARCINOMA

By far the best treatise yet written on the pathology of cancer of the uterus is that of Cullen (1900) This excellent work contains detailed histories and descriptions of many specimens of carcinomas of all types and hundreds of unsurpassed illustrations of their gross and microscopic structure by Max Brodel and Hermann Becker Hurdon's monograph (1942) is a useful outline from the clinical standpoint

Since cervical and corporeal carcinoma are aetiologically and structurally quite distinct diseases, we will consider them separately. But since mortality statistics do not separate them, we must first briefly survey the frequency of uterine carcinoma in general as disclosed in these statistics and other figures.

(I) Mortality rates, and race incidence of uterine cancer

In all countries with mortality statistics, carcinoma of the uterus appears as one of the three commonest causes of death from cancer in women, the other two being in most countries carcinoma of the stomach and carcinoma of the breast The mortality figures collected by Hoffman (1915) show that during the early years of this century, in some countries, e.g. England and Wales and Australia, uterine cancer was the commonest form of fatal malignant disease in women, that in most other European countries and in the United States of America it was second to carcinoma of the stomach, and that in all countries with reliable mortality figures, uterine cancer caused more deaths than mammary cancer Thus in England and Wales from 1908 to 1912, carcinoma of the uterus accounted for 19 673 out of 99,818 cancer deaths in females, 1e 20 per cent, as compared with 17 per cent from carcinoma of the breast and 14 per cent from carcinoma of the stomach. In Switzerland 1901 to 1910, carcinoma of the uterus caused 3,299 out of 22,593 female deaths from cancer, 1e 15 per cent as against 35 per cent from carcinoma of the stomach and 10 per cent from carcinoma of the breast In the United States of America, 1908 to 1912 cancer of the stomach and liver accounted for 34 per cent, cancers of the genital organs for 26 per cent, and cancer of the breast for 16 per cent, of cancer deaths in females

Probably owing mainly to a real increase in the frequency of curcinoma of the breast more recent mortality figures show reversal of the positions of uterine and

growths are those which appear at operation to be confined to the tube or which even though they may project at the fimbriated opening are removed intact and are found to have a uniformly high degree of histological differentiation Sulton described surgical cures in both kinds of case

Blood borne metastases in the liver lungs or elsewhere are rare

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because the precise point of origin of some adenocarcinomas of the lower uterine segment, whether endometrial or endocervical, is uncertain

Estimates of the relative frequency of the three types of carcinoma vary considerably, but broadly it may be said that cervical carcinoma is three or four times as common as endometrial and that cervical epidermoid carcinoma is at least ten times as common as cervical adenocarcinoma. Cullen a carefully studied series of 182 cases of uterinc cancer comprised 128 epidermoid carcinomas of the cervix, 35 adenocarcinomas of the corpus, and 19 adenocarcinomas of the cervix. Norris and Vogt's series comprised 346 cervical carcinomas to 115 corporeal carcinomas the latter thu, forming 25 per cent of the total (Novak cites Norris and Vogt's figure incorrectly as 15 per cent, this percentage was of all cancers of the female genital tract) Hurdon's records covered 1 340 cases of carcinoma of the cervix and 269 of the body of the uterus. My own histological material from consecutive hospital cases covers 174 cases of uterine carcinoma (144 surgical and 30 necropsy cases) which comprised 111 epidermoid carcinomas of the cervix 56 endometrial adenocarcinomas, and 7 adenocarcinomas of the cervix 1e 64 32 and 4 per cent respectively. Many of the older estimates of the frequency of corpus carcinoma are much lower than those just cited often between 5 and 15 per cent (Lane-Claypon, Kaufmann, Novak) This difference is no doubt largely attributable to the improved diagnosis of corporeal carcinoma during the last few decades especially as the result of the more regular use of diagnostic curettage with microscopical examination but it may also be partly due to a real increase in the relative frequency of endometrial carcinoma, related to its conjugal and age incidence (see below)

It is necessary to mention here the extraordinary statements made by Williams in his book on uterine tumours (1901), that of 160 consecutive uterine carcinomas only 4 were of the corpus and that most of his cervical carcinomas were of the cylinder celled 'glandular type Such a palpable error on the part of an oft quoted authority raises doubts of the dependability of all his statements on histological and statistical matters.

The estimated frequency of cervical adenocateinomas varies widely ranging in different series from 16 to 117 per cent of cervical cancers, with an average

of 57 per cent (Norris)

(4) Uterine earcinoma in animals

Uterine carcinoma is one of the Jess frequent forms of malignant disease in animals but has been seen in the rabbit, rat, mouse, guinea pig, horse ox, dog lioness boar gazelle. Intinoceros and fawn (Feldman) In all but one of these species however the uterus is a rare site of carcinoma many reported series of carcinomas in animals contain only occasional examples or none at all of uterine origin. Thus in the collection of 250 consecutive tumours in animals made by Rudduck and myself there is not an example of uterine carcinoma. The exceptional species is the rabbit in which endometrial adenocarcinoma is the most frequent form of tumour (Polson, Twort Burrows Orr and Polson). Many of the growths in other species also are endometrial adenocarcinomas, but in a few cases the tumours have been cervical in origin e.g. squamous celled carcinoma in a gazelle (Petit cited by Murray), and papillary adenocarcinoma.

mammary cancer is causes of death in England and Wales and in most other English speaking communities (see Chapter 13 and comparison tables by Hurdon) In England at present, uterine careinoma causes about 12 per cent, and mammary careinoma about 20 per cent, of the female deaths from cancer

As to the races with no reliable mortality records there is nevertheless good evidence that in these also uterine cancer is one of the commonest forms of malignant disease Medical practitioners in China and India find careinoma of the cervix a frequent form of cancer there Of 1,830 cases of carcinoma in Hindu women 888 (48 per cent) were of the gential tract and of 666 cases in Moslem women in India, 223 (33 per cent) were gential (Nath and Grewal 1935, Of 119 deaths from cancer in the Chinese of both sexes in 1937 and 1939) Hong Kong from 1895 to 1904, 14 were due to uterine cancer, of 51 eases of cancer in Hawaiians 15 were of the uterus and of 1,223 cases of cancer in coloured Cubans 347 (28 per cent) were of the female genitalia (Hoffman) The uterus is the commonest site of careinoma in native women of the East Indies (Snijders and Straub Bonne), thus in 243 cancer necropsics on Malays and Chinese in Java and Sumatra, Bonne found 31 cases of uterine carcinomy of which 25 were in Malays Cervical cancer is frequent in the Chinese of Hainan (Bercovitz, 1941), in American negresses (Cullen Quinland and Cuff) and in Nigerian natives (Smith and Elmes) There is good evidence that cancer of the uterus is less frequent in Jews than in non Jews of the same community (Hoffman . Sorsby Smith)

(2) Mortality from uterine cancer in relation to age and conjugal state

We shall see later that carcinoma of the cervix and carcinoma of the corpus differ markedly in both their age incidence and their relation to conjugal state and parity. Here however, something must be said of the age distribution of uterine carcinoma as a whole and its relation to conjugal state as disclosed by mortality statistics The 76th Annual Report of the Registrar General for England and Wales (1915) contained an informative analysis of the deaths from uterine cancer for the 3 years 1911 to 1913 setting out the standardized mortality rates for the successive 5 year age periods from 25 onwards for both single and married or widowed women. This analysis showed clearly (a) that for both the single and married groups the mortality rate rose throughout life until old age, when there was a slight falling off in the rate (b) that at all age periods the mortality rates for married women decidedly exceeded those for single women the differences being much more marked before than after the age of 50 and (c) that the standardized rate for all ages over 15 years was 73 per cent greater for the married than for the single Further analysis of age distribution and relation to conjugal state and parity is best made from accurate clinical records and with respect to the three main types of carcinoma now to be discussed

(3) The three types of uterine carcinoma and their relative frequency

Carcinomas of the uterus fall into three groups—(1) epidermoid carcinoma of the cervix (2) endometrial adenocarcinoma of the corpus and (3) adeno extenoma of the cervix Groups (1) and (2) are quite distinct in their incidence structure and behaviour group (3) is less sharply separable from group (2)

(3) Mode of origin, pre-cancerous and early cancerous changes Most epidermoid carcinomas of the cervix arise directly from the stratified epithehum of the external os or the portio vaginalis (Fig. 249)



Fig. 249—Very early superficial epidermoid carcinoma of the cervix of a woman of 40. The tumour is of uniform death coars considerable and

the origin may be from metaplastic stratified epithelium formed within the cervical canal or glands or in an endocervical polypus (Fig. 250)

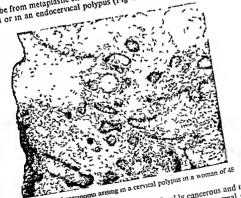


Fig 250 —Early epidermoid carcinoma arising in a cervical polypus in a woman of 48 (× 80) In addition to early growths which are already frankly cancerous and invasive when they first come under notice, there occur also various abnormal changes in the covered embedding the records as a control of the most the covered embedding the records as a control of the mist.

when they arst come under notice, there occur also various abnormal changes in the cervical epithelium the possible pre cancerous proclivities of which must

in a rhinoceros (Betke) Bullock and Curtis described squamou celled careinomas of the uterus in rats

EPIDERMOID CARCINOMA OF THE CERVIX UTERI

(1) Age incidence

The age distribution of cervical carcinoma is similar in all European countries and the collected results of 7.381 cases (Lane Claypon 1927) showed the following approximate percentages in successive 5 year periods

| Ages - | - | Under 30 | 30~ | 35- | 40- | 45~ | 50~ | 55- | 60~ | 65- | Over 70 |
|-------------|---|----------|-----|-----|-----|-----|-----|-----|-----|-----|---------|
| Percentages | - | 4 | 9 | 16 | 20 | t9 | 15 | 9 | 5 | 2 | t |

Thus about two fifths of the cases were in the fifth decade, and the mean age was 46 years. The ages recorded in many other individual series of cases (Cullen. Pack and Le Fevre and my own) are in close agreement with this the maximal number of cases occurring in the fifth decade and the mean age of onset falling between 45 and 50 years—47 in my own series. This mean age is earlier by several years than in most other classes of carenoma namely of the breast stomach intestine oesophagus and mouth in all of which the mean ages of onset he between 50 and 59 (Greenwood 1926). In more than one half of the cases cervical earenoma commences in the age period 40-55. It shows no relationship to the menopause, the mortality curves rising steadily to old age. It is rarely seen under the age of 25, but has been recorded in minors of (Diddle). It is also rare after 65. Patients in the younger age groups show neither lower operability nor worse prognosis than older patients (Lane Claypon). The mean duration of untreated cases is about 21 months (Lane Claypon).

(2) Marital state, parity, menstrual history

It has long been recognized that earcinoma of the cervix is less frequent in single and nulliparous than in parous women. Thus of Cullen's 50 cases with the necessary details recorded all were married and only one was childless. Of 7986 cases collected by Lane Chaypon only 170 (21 per cent) were single. Lane Chaypon and McCullagh found that about 9 per cent of cases of cervical careinoma were nulliparous. These figures contrast sharply with those for careinoma of the corpus (see below)

While parity thus decidedly predisposes to cervical cancer the number of pregnancies appears to be immaterial. Lane Chypon's analysis showed that the incidence of the disease was no greater amongst mothers of many children than amongst mothers of few or only one and also that miscrirages did not specially predispose to cervical eliteriomi. The previous menstrual histories of pitients show no significant differences from those of non-cancerous women

Occasional early specimens of cervical carcinoma afford evidence, similar to that described for the skin and hp, that the growth has arisen, not from a single minute focus but from a considerable field of epithelium (Fig 249). Even in already well-established growths, histological evidence that cancerous change of the neighbouring epithelium is still in progress may sometimes be seen, as in several of Cullen's carefully studied cases e.g. that depicted in his Fig. 42. Clear instances of cervical carcinoma of multicentric origin have not so far been described. There is need of further careful studies of the mode of origin of early carcinomas in this region by serial sections and reconstructions.



Fig. 251—Great cellular and nuclear pleomorphism in epidermoid carcinoma of the cervix (× 80)

(4) Structure

As in other sites epidermoid caremoma of the cervix may appear as a projecting papillary growth, or as an infiltration of the underlying tissues with early surface ulceration, or as a combination of these two drawings in Cullen's book fully illustrate the various gross and microscopic appearances of the tumours

Microscopic structure

Although distinct epidermoid differentiation of some degree is to be found in most of the growths they present a wide range of histological appearances. The degree of keratinization, the size and shape of the cell clumps, and the characters of the cells and their nuclei, all vary greatly. Cornification in the form of well defined cell nests is less frequent than in oral and epidermal carcinomis, but patchy irregular keratin formation is frequent. The cell clumps are often large and of triangular lentiform or irregular outlines in section, fine tendril like growth of the epithelium is rare. The structural peculiarities of the individual

be considered. These include hyperplastic and metaplastic changes accompanying cervicitis ecosions, polypi and leucoplakia. The earlier literature and views on this subject were well outlined in 1916 by Stone who gave examples of the various pre cancerous. lesions and who concluded that for each type of fully developed carcinoma there is a corresponding type of benign and intermediary change. Schiller (1928) also depicted many examples of suspicious cervical lesions discovered by routine examination of excised uteri, and he concluded that these were indeed early carcinomas comparable with Bowen's disease of the skin. Smith and Pembetron described 16 early cervical exerionemas

However the pre cancerous potentialities of histologically suspicious changes have certainly been evaggerated. Squamous metaplasia of the endocervical glands producing appearances resembling early carcinomatous invasion are common and are innocuous in the great majority of cases. Carmichael and Jeaffreson found such changes in 40 per cent of adult cervices attributed them to both hormonal and local factors, and rejected the view that they are pre cancerous. Close familiarity with the histological variations possible in normal and damaged cervices at all ages is necessary before attempting to assess the significance of suspicious epithelial changes in this region. Undoubtedly many of the supposedly 'pre cancerous. Icsions of the cervical epithelia are harmless, and the distinctive characters of the truly pre cancerous states have yet to be defined.

The infrequency of epidermoid carcinoma of the cervix in nullipara strongly suggests as Cullen said ' that the injuries incidental to labour have a potent influence on the development of this variety of cancer. Very plausibly then tears erosions and cervicitis have been postulated as the exciting or predisposing factors However, this proposition also is far from established. The acknowledged rarity of carcinoma of the cervix of the prolapsed uterus shows that simple mechanical irritation and persistent mild inflammation are in themselves not important factors in the causation of cervical carcinoma. Nor is there any evidence that venereal infections predispose to this disease. It seems likely then that the parous uterus is prone to the development of cervical careinoma for some more specific reason than the more presence of the effects of trauma or chronic inflammation. The factors concerned are still obscure, but that hormonal as well as local factors may be concerned is strongly suggested by the experimental production of cancer of the cervix in mice by prolonged oestrogen administration (see Chapter 4 Section V) The suggestion that coitus may play a direct part lacks evidential support as does also the view that contraceptive practices may be partly responsible. That the development of careinoma of the cervix is not dependent on the presence of the body of the uterus is shown by the frequency of this di case in the residual cervix after subtotal hysterectomy for myomas and other diseases. Behney cites figures from various writers showing that stump carcinoma develops in between 01 and 6 per cent of cases of subtotal

stump careinoma develops in between 01 and 6 per cent of cases of subtortal hysterectomy figures which show no clear evidence of either increased or diminished liability of the residual cervix to cancer. Simultaneous separate careinomas of the cervix and corpus are occasionally seen. I have examined two

specimens showing this coexistence

Occasionally, however, diffuse spindle celled carcinoma may simulate sarcomatous appearances. There is no doubt that many cases of supposed "sarcoma" and endothelioma of the cervix, such as those depicted in Cullen's Figs 102 to 104 and 178 and 179, have been instances of diffusely cellular or otherwise atvipical carcinoma. Cullen himself, indeed, with scientific frankness, reported a case of squamous celled carcinoma of the cervix microscopically resembling sarcoma in places of which he said, "were it not for sections from other portions of the growth in which the squamous-cell origin is clear, one would be justified in making a diagnosis of sarcoma."

Some cervical carcinomas of rapid growth and poor keratinization show well defined rounded intra epithelial spaces, formed partly by fluid accumulation and partly by degenerated cells (Fig 253) Cursory microscopical examination of such a tumour may easily lead to an erroneous diagnosis of 'adenocarcinoma', but closer inspection will show that the epithelial masses are of epidermoid type and that there is no true glandular orientation of the cells around the spaces

The great cytological diversity exhibited by cervical carcinomas renders attempts at precise grading" even more arbitrary and futile here than in other situations (Willis, 1931) While carcinoma cells may sometimes be identified in vaginal smears (Gates and Warren), I feel very dubious of the diagnostic reliability of this test in most cases

Eosinophil leucocytes sometimes collect in great numbers in and around epidermoid carcinoma of the cervix (references, Willis, 1934), and occasionally pronounced cosinophilia of the blood also develops (Sala and Stein) Metaplastic ossification of the stroma of the growth, as in Reich's third case, is rare

(5) Local spread

Following infiltration of the cervix itself, extension of the growths may take place in any direction Extension downwards into the vaginal walls is frequent and necessitates removal of a liberal vaginal cuff in performing hysterectomy Cranial extension into the body of the uterus sometimes effects almost complete replacement of the organ Of great practical importance is the occasional growth which ascends far into the corpus without producing conspicuous changes in the portio vaginalis. The pelvic peritoneum may be reached by cranial extension and transcoelomic metastases may arise in this way. Lateral extension into the parametrial tissues is of great importance, since on its extent operability and prognosis largely depend. In advanced cases the growth reaches the walls of the pelvis and produces fixity of the viscera Obstruction of the ureters is common and death is often due to ascending renal infection. Anterior and posterior spread involves the bladder and rectum, and fistulae of these are distressingly common in late stages of the disease The invasion of pelvic veins by growth is sometimes demonstrable (Reich) Of occasional results of the direct spread of cervical cancer may be mentioned pyometra, sometimes perforating and causing periton itis, direct spread from the parametrium to the tube or ovary, sometimes with invasion of ovarian cysts, contact invasion of adherent coils of intestine sometimes causing intestinal obstruction (Willis, 1931), and invasion of uterine myomas (e.g. Cullen s Figs 72 and 74)

cells are legion and often very diverse in one tumour, multinucleated cells and giant nuclei of bizarre shapes are common (Fig 251) Many tumours contain

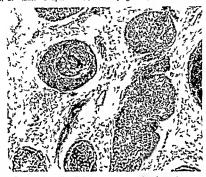


Fig. 252 —Undifferentiated spindle-celled clumps in a cervical epidermoid carcinoma (× 96)



Fig. 253—Rounded spaces in a very cellular rapidly growing epidermoid careinoms of the cervis these had led to an incorrect histological diagnosis of "adenocarcinoma" (> 300)

glycogen rich clear cells a good description of which is that of Babes and Lazarescu Pantzu. Some tumours show a prominent spindle-celled structure the spindle cells usually forming well-defined epithelial clumps (Fig. 252)

thoracic and cervical glands Esumates of the frequency of lymph nodal metas tases vary widely In necropsy series they he usually between 50 and 70 per cent, in surgical series between 25 and 45 per cent. Thus Williams found lymph glands affected in 56 of 78 necropsy cases of uterine cancer (nearly all cervical) 1 e 72 per cent. Of my 23 necropsy cases, 12 (52 per cent) showed discrete deposits in glands Bonney found glands affected in 42 per cent of operation cases. From deposits in the upper lumbar lymph glands the thoracic duct may be invaded and, next to gastric carcinoma, uterine (mainly cervical) carcinoma is the most frequent invader of the duct, accounting for about one quarter of the cases (Willis, 1934). Main veins may be invaded from contiguous cancerous lymph glands, e.g. the inferior vena cava in one of my cases (1931, Case VII)

(b) Metastases by the blood stream

These are found in about one quarter of fatal cases, most commonly in the liver or lungs Metastasis to the liver probably occurs usually by the portal vein, following invasion of veins in the wall of the rectum or neighbouring perito neum, the lungs are reached by way of the systemic veins or the thoracic duct Blood borne metastases in other parts are rare, but bones occasionally contain metastases, which may even minic primary tumours (Williams, Kaufmann, Joll, Reich and other references by Willis, 1934)

(c) Metastases in ovaries, tubes and vagina

On rare occasions, apparently discrete secondary growths have been seen in the ovaries or tubes, e.g. by Borrmann, Culten (Figs. 78 and 84). Taussig Bell and Datnow, and Reich. The route of origin of these deposits is uncertain and indeed it is usually difficult to be sure that they are indeed separate from the main tumour and not merely outerops from inconspicuously infiltrated tissues. When genuinely separate, they may have arisen either from venous or lymphatic emboli carried by aberrant routes because of obstruction of main vessels in the parametrial tissues, or from particles of tumour carried retrogradely within the lumen of the Fallopian tube, or by transcoelomic metastasis on the ovarian or tubal surfaces following extension of the primary growth to the serious surface of the uterus or to the pouch of Douglas. Seemingly discrete nodules of growth, sometimes seen in the walls of the vagina are often not true metastases but merely outcrops from inconspicuous infiltration of the underlying tissue. When really discrete they must be attributed to downward carriage of tumour emboli in venis or lymphatics following blockage of these vessels higher up, it is extremely improbable that implantation of tumour cells on the vaginal surface occurs.

ENDOMETRIAL ADENOCARCINOMA OF THE CORPUS

(1) Age incidence

All statistics agree that corporeal careinoma occurs decidedly later in life than cervical on an average about 8 years later (Cullen, Norns and Vogt,

The following remarkable case exemplifies slow extensive superficial spread of a cervical carcinoma in the endometrium, tubes and ovaries

Case I (Mr. R. Fowler s. case) —History.—În 1934 at age of 48 patient had ulerine haemorrhages was cureited and found to have squamous-cell carcinoma of the cervical canal the growth consisting of thick layers of poorly cornifying stratified epithelium spreading over available surfaces but also invading subjacent tissues. Radium was introduced with good local effect. Patient then remained well until September 1934 when a lower abdominal mass was noticed disclosed large right ovarian cyst was maller left ovarian cyst unbest uterus appeared normal. Laparotomy disclosed large right ovarian cyst was maller left ovarian cyst unbest uterus appeared normal to tubes and cysts were removed. Noked-eye examination—Right sided cysts 2 in number were 10 and 4 centimettes in diameter espectively unioned by a wast of indigrated tissue I centimetre thick and 3 centimetres.



Fig. 254—Case I. The even layer of non-cornifying epidermoid carcinoma lining the right Fallopian tube. (× 120)

wide cysts were thin walled had smooth fibrous outer coats and were lined by a thin layer of irregularly corrugated papillary growth right tube was irregularly thekened in its outer half and adherent to smaller cyst wall. Left sided cyst was 3 centimetres in diameter and generally similar to those on right side except that it showed some papillary projections from its outer surface attached tube was indurated but not enlarged blicro-examination unexpectedly recalled that the whole of both Fallopian tubes the larger right sided cyst and the left sided cyst were all hine by a layer of non-comifying strainfed cytichlum resembling that of the cervical growth examined 10 years earlier (Fig. 234). Ovarian tissue was present on one side of each of the cysts which appeared to be tube ovarian cysts developed as a result of the growth spreading out of the abdomination of the tubes. The smiller right sided cyst was then by cubical epithelial cells and was probably a simple partovarian cyst. (Note—The surgeon decided not to remove the uterus but to apply radiational treatment.)

(6) Meiastasis

(a) Lymph nodal metastases

In parametrial invasion both direct spread and embolic metastasis to lymph glands share. Later the disease spreads to the lumbar inguinal and even the

(2) Marital state, parity, menstrual history

Unlike carcinoma of the cervix, corpus cancer often occurs in the single and nulliparous. Thus of 19 of Cullen's cases with the data recorded although 17 were married, 10 had never been pregnant, in Norris and Vogt s series 26 per cent were spinsters. Lane Claypon and McCullagh found not less than one third of all cases to be sterile for one reason or another, and in Miller's series, of 183 cases, 177 of whom were married, 48 (i.e. 27 per cent) had never conceived Thus, while childbearing predisposes to carcinoma of the cervix, sterility or some factor related to it predisposes to endometrial carcinoma. The menstrual histories of subjects of this disease show no significant abnormalities.

(3) Inherited predisposition to corpus careinoma

While the family histories of most cases of uterine carcinoma do not suggest any inherited tendency to the disease, some striking exceptions are recorded. The most remarkable of these is the 'Family G'' first described by Warthin (1925), and later by Hauser and Weller (1936). In this family, in the course of three generations, 41 persons out of 174 aged 25 or more produced 43 carcinomas. All of the 20 cancers in males were gastro intestinal, while the 23 cancers in females included 6 gastro intestinal and 15 endometrial, no case of cervical carcinoma occurring.

(4) Pre-cancerous conditions in the endometrium

Lesions which have been held to predispose to endometrial carcinoma include endometritis, hyperplasias polypi and myoma Let us consider each of these

(a) Endometritis

The suggestion of early writers that endometritis predisposed to cancer of the uterus was largely due to a misconception of what constituted endometritis With increasing recognition of the distinction between true infective endometritis and non inflammatory endometrial hyperplasias well outlined by Kaufmann, attention has shifted from the former to the latter as possible pre cancerous states. There is no evidence that post abortal puerperal or venereal infections predispose to endometrial cancer, and the occasional coexistence of cancer and tuberculosis in the uterus (von Franqué, Gais) is probably merely coincidental

(b) Endometrial hyperplasias

These form a large and diverse group doubtless related in most cases to hormonal disturbances, though the exact nature of these is often obscure. There are good grounds for believing with Novak (1941) and others that in some cases initially simple hyperplasia passes into carcinoma. This applies particularly to post menopausal hyperplasias. The grounds for this belief are as follow (i) As Kaufmann. Stone Welsh. Novak and others have pointed out there is no sharp histological borderline between hyperplasia and carcinoma. While it is fortunately true that in the great majority of cases the microscopical diagnosis of one or the other can be made confidently, there occur eases in which the most experienced are unable to distinguish between extravagant atypical hyperplasia

Lane Claypon, Pack and Le Fevre) Thus, Norris and Vogt's series of 115 cases with a mean age of 53 showed the following age distribution

| Decade ~ ~ | - | 3 | 4 | 5 | 6 | ŧ | 7 | 1 | 8 | |
|-------------------|---|---|-----|----|----|---|----|---|---|---|
| | | | 4.4 | | | | | | | ~ |
| Number of cases - | - | 1 | 14 | 18 | 57 | | 21 | 1 | 4 | |

The mean age of Miller s 183 cases was 54, and of Pack and Le Fevre s cases 55, as compared with 48 years for carenoma of the cervix. In my own series of 31 specimens from patients of recorded ages, the mean age was 57 years at the time of operation, compared with 48 for cervical carenoma.

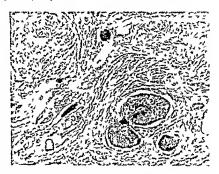


Fig. 255 — Case II — Solid careinomatous clumps of an adenocareinoma occupying small veins in the myometrium $(\times 60)$

Carcinoma of the corpus is rarely seen under the age of 30 the youngest of Norris and Vogt's series was 29 and the three youngest in my series were 25 32 and 41. The disease has appeared however, even in childhood and adolescence (Gilbert, Diddle). Unlike cerucal carcinoma that of the corpus often appears after the age of 65. this applied to 9 of my 31 cases. The youngest patient in my series presented some other unusual features justifying a brief summary.

Case II —A single woman aged 25 who had had no menstrual abnormalities and who was otherwise in good health complained of lower abdominal discomfort of 3 months duration. Operation showed multiple terrine myonats the Lingett the size of a tennis ball, subtotal hysterectorn was performed. Examination of the specimen unexpectedly exceeded in addition to the myonate a bulky endometrial growth microscopically an active adenocatronoma with areas of solid anaplastic growth which extraded into the muscle and myaded small blood vess-ls (Fig. 255). In one of the features, the patient remained well and with no signs of recurrence 5 years later.

carcinoma are found together at an early age, certainly support this idea. Careful statistical study of the frequency of the coexistence of myoma and carcinoma is needed before deciding whether this is wholly fortuitous or not

(5) The mode of origin of endometrial carcinomas

There is good evidence that, as in many other epithelia, so in the endometrium, carcinoma often arises from a more of less extensive field of tissue sometimes purhaps the entire endometrium (a) As already noted above, clear histological evidence of the progressive transformation of hyperplastic endometrium into

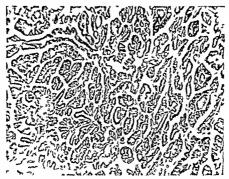


Fig 256—From a bulky endometrial carcinoma, showing the complex tubular pattern frequently seen in these growths (× 20)

carcinoma is sometimes to be seen (Novak) (b) Specimens are not unusual in which much or the whole of the endometrium is replaced by a superficial layer of carcinoma with little penetration into the muscle, and it seems much more likely that these have arisen by an extensive cancerization of the endometrium us situ than by spread from a single small focus (Welsh) (c) Multiple foci of carcinoma are sometimes seen, these have been attributed to regional metastases in the endometrium (Kaufmann) but they more probably denote multifocal origin. Careful study of the endometrium and of early carcinomas in predisposed families, such as the "Family G', of Warthin would probably afford particularly clear evidence of the mode of origin of these tumours

(6) Structure

Again Cullen's work provides an admirable atlas of the gross and minute anatomy of the discuse. Many of the tumours are well differentiated columnar-celled adenocarcinomis often with convoluted tubular or papillary patterns (Fig 256) Areas of solid epithelial masses are also common, and these or still more anaplastic diffusely cellular growth may form most of the tumour. However

and commencing careinoma (ii) Hyperplasia and carcinoma may coexist with apparent transitions from one to the other. Novak depicted examples and stated that he had observed the coexistence in nearly one quarter of his cases of adenocaremona Early adenocatemona has been observed arising in an extensively hyperplastic endometrium (Fluhmann and Stephenson) Kaufmann referred to cases of intramural adenocarcinoma arising from the epithelium of adeno te that type of endometrial hyperplasia now called endometriosis Oldfield and Stewart also described an example of carcinomatous endometrious interna, and I have seen a closely similar specimen (iii) In rare cases cited by Fluhmann and Stephenson repeated curettings have shown at first only hyperplasia but later caremoma (iv) By analogy with other organs under endocrine control such as the breast pro tate and ductless glands themselves it would be surprising if atypical hyperplasias of the endometrium did not at times become neonlastic. While much experimental investigation of the endometrial overgrowths produced by excessive oestrogens has been carried out we still await elucidation of all the hormonal and local factors responsible for human endometrial hyperplasias and for determining the transition to neoplasta in some cases. The predisposition of single and childless women to endometrial carcinoma as compared with cervical carcinoma is no doubt related in some way to the unphysiological life of the unproductive uterus

(c) Endometrial polypi

Polypi are an occasional source of careinomas (Iseki, cited by Novik) Malig nant change in a previously being polypismust be distinguished from circinoma beginning as a loculized polypiod growth. When cases of this kind and polypi of doubtful malignancy are excluded very few examples of careinoma commencing in polypi will remain. If we look upon polypi as being tumours—adenomas or appillomas of the endomertrium—their malignant change in them painfiles that seen in polyposis of the stomach or intestine. If we look upon polypi as localized hyperplasias, then supervening careinoma will appear as a special instance of the socuence discussed in the previous priractable.

(d) Myomas

The coexistence of uterine myoma and carcinoma has frequently been noted (many examples by Cullen) and when the carcinoma has occupied the endometrium immediately overlying a projecting submucous imyom; the tempta tion has been strong to suppose that the latter has induced the former. But in view of the great frequency of uterine myomas (perhaps in about 20 per cent of woman over 30) we must strongly suspect their coexistence with carcinoma to be only coincidental in most cases. However, an indirect relationship between the genesis of myoma and of endometrial carcinoma is quite possible. It is not unlikely that uterine myomas are related to hormonal disturbances in which oestrogens play a part, and we have just noted the pre-cancerous potentialities of some endometrial hyperplasias many of which also are cert inly the result of hormonal disturbances. Perhaps then in some cases of coexisting myoma and carcinoma both tumours may owe their genesis to a common hormonal factor. Cases like No. It above in which multiple large myomas and endometrial.

of such areas only It is significant that no eases of pure epidermoid carcinoma of the endometrium have been recorded of recent years. Kaufmann has given a valuable outline of squamous metaplasia in uterine carcinomas, and of the possible relationships of carcinomas to previous squamous metaplastic changes in the uterus. In my opinion squamous metaplasia in the endometrium should always be regarded as carcinomatous.

Some endometrial carcinomas are so anaplastic that little or no trace of glandular differentiation is to be found. Descriptively we must call these "carcinoma simplex", though of course it is not implied that they are essentially any different save in degree of anaplasia, from the adenocarcinomas. Usually such growths consist of polyhedral cells arranged in recognizably epithelial clumps, but sometimes they become quite diffuse in structure. Elsewhere (1931 and 1932) I have given instances of the way in which anaplastic areas of uterine adeno carcinomas may become diffusely cellular, simulating sarcoma microscopically. The same topic is discussed and well illustrated in a valuable paper by Tudhope and Chisholm who emphasize the wide range of structure possible in anaplastic endometrial carcinomas and who rightly doubt the genuinenes of many supposed instances of sarcoma and carcino sarcoma of the uterine cavity. In his Fig. 78, Nicholson (1924) depicted cartilagmous metaplasia in the stroma of an endometrial carcinoma.

(7) Growth and local spread of endometrial careinoma

In their early stages many carcinomas are quite superficial and largely confined to the endometrium itself over a small or large area. As Novak pointed out, and as I myself have repeatedly confirmed, it is not unusual for diagnostic curettage to lead to a microscopic diagnosis of undoubted carcinoma. hysterectomy to be performed soon afterwards, and for careful examination of the uterus to fail to discover any residual growth. Of course it must not be concluded from such cases that curettage alone has indeed eradicated the growth, undiscovered residues may be present in parts not examined, for serial microscopic examination of an entire uterus is impracticable. In other cases, when curettage has been less complete minute residues of tumour, still, however, confined to the endometrium may be found in the excised uterus. In one such specimen, in which no residual tumour could be found in the uterine cavity, I discovered a small cancerous focus in the myometrium close to the entry of a Fallopian tube.

In more advanced stages the tumour may spread over much or the whole of the endometrial surfaces, distend the cavity, penetrate to a variable depth into the muscle, and produce enlargement of the uterus. Direct extension into one or both Fallopian tubes may take place. The tumours may also spread downwards in the cervical canal and may protrude into the vagina. Uterine myomas may be invaded (see Cullen's Fig 433)

Deep invasion of the muscle and extension to the peritoneal surfaces and to the parametria are late usually irremediable, stages of the disease often accompanied by great enlargement of the uterus, spread to neighbouring organs and metastases in lymph glands or peritoneal cavity. Rectal and vesical fistulae are much less frequent than with cervical carcinoma.

no distinction in nomenclature between the variants is called for they are all endometrial carcinomas with varying degrees of differentiation. In particular as Kaufmann rightly insisted the old self-contradictory name "adenoma malignum" still retained by some writers for the best differentiated members of the group (as by Ewing) should be discarded

One variety of structure seldom mentioned shows areas of clear cells and closely resembles clear-celled papillary adenocarcimoma of the kidney. The nature of the change in the cytoplasm which produces this appearance is uncertain, it is not due to the presence of mucus and selective stains for glycogen or fatty substances have been mapphicable to the few paraffin-embedded specimens which I have examined



Fig. 257—Islands of squamous epithelium in the glandular spaces of an endometrial adenocarcinoma from a woman of 63 (× 60)

Epidermoid metaplasia is a frequent change in parts of the tumours (Fig. 257) It was observed in 9 of my 50 cases a proportion closely similar to Miller's figure of 15 per cent Nicholson (1923) found squamous epithelium in 14 of 36 endometrial carcinomas Such tumours have often been called adeno acanthomas In behaviour and prognosis they differ little if at all adeno cancroids from other endometrial carcinomas. Some earlier writers on uterine carcinoma described examples of what they believed to be pure squamous celled carcinomas of the corpus e.g. Gebhard (1892) Flasschien (1895) and Emanuel (1895) While it is not impossible that predominantly or even exclusively epidermoid careinoma of the endometrium may occur this diagnosis can of course be sustained only after thorough microscopic study of all parts of the tumour and after exclusion of the possibility that a cervical careinoma has extended up into the corpus as Emanuel admitted may have happened in his case. These early workers were not aware of the frequent occurrence of areas of squamous metaplasia in adeno cureinomas of the uterus and they may have ben misled by microscopic study

(c) Transpersioneal metastasis

Once the tumour has reached the peritoneal surface at any point either of the uterus itself or by the transtubal route, metastasis to other parts of the peritoneum readily takes place. Discrete peritoneal metastases are present in about one half of fatal cases.

(d) Metastasis by the blood stream

With rare exceptions, blood borne metastases appear only late in the course of the disease—they are present in only about one quarter of fatal cases. The organs most often affected are the lungs, liver and bones. The metastases are rarely of any clinical importance but occasionally those in bones create diagnostic difficulties. Thus Kaufmann mentioned a case with widespread metastases in which the only symptoms had been pains due to spinal denosits.

(e) Metastases in the vagina and vulva

These have been described by many writers, e.g. Cullen (Figs. 218-9). Strachan and Spencer, and have often been attributed to surface implantation. I also have seen apparently discrete vaginal nodules which could plausibly have been supposed to have arisen in this way. It is, however, very doubtful whether such grafting of tumour particles on the vaginal surface ever occurs. As Kaufmann, Milner, Sampson Leitch and others have insisted for cervical cancer, lymphatic extensions of the growth into the vaginal walls are frequent, and this applies also to advanced corporeal growths. Outcrops from these extensions or from embolic tumour particles arrested in lymphatics or small veins in the subepithelial tissues are undoubtedly the cource of most or all of the supposed vaginal implants from uterin cancers, endometrial and cervical alike. Spencer described two remarkable cases of endometrial carcinoma with metastases in the vagina and vulva, treated by operation and radiation, and free of recurrence after 10 and 13 years respectively.

ADENOCARCINOMA OF THE CERVIX

Since the exact site of origin of growths within the cervical canal or isthmus is seldom. Anown, and since adenocarcinomas are seldom of such distinctive histological structure that the specific nature of their parent glandular tissue is clear, the scope of the name adenocarcinoma of the cervical glandular epithelium proper, but there is little doubt that there have often been included in this class endometrial adenocarcinomas of the isthmus or lower part of the body which have sprend downwards into the cervical rough of which is sure are (a) those in which the endometrium of the isthmus is demonstrably uninvolved and (b) those the microscopic structure of which clearly resembles cervical rather than endometrial glandular tissue, especially mucus secreting growths. It is also possible that some adeno papillary growths of the cervic may arise not from the cervical glands proper, but from the neighbouring remains of Gartner's duct (see a report by Wolfe and further discussion in the next chapter). These uncertainties as to precise origin must be borne in mind when reading accounts of cervical adenocarcinomas", the best of which are those of Cullen and Norris.

(8) Metastasis

In general endometrial carumoma metastasizes relatively late Metastasis in the five following ways must be considered (a) by lymphatics (b) by the Fallopian tubes, (c) by the peritoneal cavity, (d) by the blood stream, (e) by surface implantation in the vagina

(a) Metastasis by lymphatics

Deposits in lymph glands are usually absent as long as the tumour remains confined to the uterine cavity or extends only superficially into the muscle, but they are often present when the muscle is deeply invaded, or the tumour has reached the parametrium or peritoneum. The glands first affected are those of the hypogastric iliac and lower lumbar groups. Extension to more cranial groups may follow but in general this is less pronounced than with cervical careinoma and involvement of the esterna chyli and thoracic duct is rare. Many authorities eg. Novak, have believed lymphatics to be the principal route of metastasis to the tubes and ovaries but while this may be admitted for some cases my own findings satisfy me of the greater importance of the tubal route, now to be described.

(b) Metastasis by the Fallopian tubes

Kundrat Werner, Sampson Offutt and others have advanced clear evidence that detached fragments of carcinoma of the fundus of the uterus may pass into the lumina of the tubes to be implanted there or on the ovaries or pelvic peritoneum I have seen several specimens which convince me that this is a frequent mode of metastasis of fundal carcinoma. Thus in one ease a surgically excised uterus contained a large adenocarcinoma which involved the cornua and uterine ends of both tubes the surfaces of both ovaries presented many raised nodules up to 3 millimetres in diameter, histological study of which showed them to be adenocarcinomatous implants mounted on the surface of the ovaries the substance of which was clear of growth. In another surgical specimen, the fundus was distended by a large adenocarcinoma which invaded the muscle but nowhere reached the peritoneum and which involved the medial ends of both tubes. The remainder of the tubes and the broad ligaments and mesovaria were clear of growth and this was confirmed microscopically Each ovary was replaced by a single thin walled serous cyst, and on the surface of the cystic right ovary just below the fimbriated end of the tube there was a single pedunculated nodule of adeno carcinoma 4 millimetres in diameter. In yet another case, the fundus contained a friable adenocarcinoma which extended only slightly into the muscle lumen of the middle part of the right Fallopian tube was occupied by a discrete nodule of growth 8 millimetres in diameter and the right ovary and adjacent omentum contained large multiple masses of secondary growth. In my opinion so real is the risk of transtubal metastasis from fundal carcinoma that the surgeon performing hysterectomy for this disease should (a) make a special search for early metastatic nodules seeded on the ovaries fimbriae or neighbouring peri toneum discovery of which will decidedly affect prognosis and (b) exercise all possible care during the operation to avoid undue pressure on the uterus and tubes so minimizing the risk of expressing fragments of growth from the tubes into the peritoneal eavity

(c) Transperitoneal metastasis

Once the tumour has reached the peritoneal surface at any point, either of the uterus itself or by the transtubal route, metastasis to other parts of the peritoneum readily takes place. Discrete peritoneal metastases are present in about one half of fatal cases.

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With rare exceptions, blood-borne metastases appear only late in the course of the disease, they are present in only about one quarter of fatal cases. The organs most often affected are the lungs, liver and bones. The metastases are rarely of any clinical importance, but occasionally those in bones create diagnostic difficulties. Thus Kaufmann mentioned a case with widespread metastases in which the only symptoms had been pains due to spinal deposits.

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ADENOCARCINOMA OF THE CERVIX

Since the exact site of origin of growths within the cervical canal or isthmus is seldom known and since adenocarcinomas are seldom of such distinctive histological structure that the specific nature of their parent glandular tissue is clear the scope of the name adenocarcinoma of the cervix' is uncertain Strictly it should refer only to tumours arising from the cervical glandular epithelium proper, but there is little doubt that there have often been included in this class endometrial adenocarcinomas of the isthmus or lower part of the body which have spread downwards into the cervix. The only tumours the genume cervical origin of which is sure are (a) those in which the endometrium of the isthmus is demonstrably uninvolved and (b) those the microscopic structure of which clearly resembles cervical rather than endometrial glandular tissue especially mucus secreting growths. It is also possible that some adeno papillary growths of the cervix may arise not from the cervical glands proper, but from the neighbouring remains of Gartner's duct (see a report by Wolfe and further discussion in the next chapter). These uncertainties as to precise origin must be borne in mind when reading accounts of cervical admocarcinomas the best of which are those of Cullen and Nortis.

(1) Frequency

Norns s paper tabulates many reported series of cases of cervical carcinoma, totalling 9 509 cases of which 542 (i.e. 57 per cent) were adenocarcinomas. The percentage in different series however differed greatly, from 16 to 117, owing no doubt to the uncertain limits of the group. Griffin found 94 of 749 cervical carcinomas (126 per cent) to be of glandular type.

(2) Age

The average age of Norris s 43 cases was 47 two thirds of them were in the fill and sixth decades and the youngest was 28. Cullen also found the disease to occur most often between the ages of 45 and 50 years.

(3) Marital state

Of 13 of Cullen's cases 12 were married and had borne children. Of Norris's 43 patients 38 were married or widowed and 80 per cent had been pregnant or had had operations on the cervix. Unlike endometrial adenocarcinoma, there is no evidence that sterlity predisposes to cervical admocarcinoma.

(4) Macroscopic appearance

This varies widely the tumours may be ulcerated papillary nodular or diffusely infiltrating and they may arise in the vaginal part of the cervix, within the cervical canal or intramurally

(5) Microscopic structure

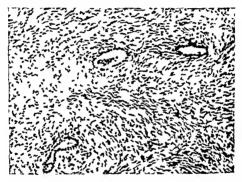
Noris s many excellent figures sufficiently show the wide range of structure and the impossibility of making any useful sub-division of the group Tumours of mingled epidermoid and glandular structure, adeno acanthomas Mucus secretion by the tumour cells also appears to be infrequent but when it is present it affords the most substantial evidence of the genuinely cervical origin of the tumour Elsewhere (1931) I have recorded an example of well differentiated mucoid adenocarcinoma of the cervix and Griffin described two cases of this kind. Cullen described an unusual case of mucoid adenocarcinoma widely involving both cervix and corrus with great enlargement of the uterus.

(6) Growth and metastasis

In behaviour and prognosis the tumours more closely resemble cervical epidermoid carcinoma than endometrial adenocarcinoma. In many cases there is early infiltration of the cervix spread to the parametria and metastasis to regional lymph glands. However again the uncertain limits of the group make it futile to attempt to generalize about its behaviour or to calculate the frequency of metistasis. In the only case of undoubted cervical adenocarcinoma on which I performed necropsy referred to above the large growth had directly invaded the appendix and ileum there were metastases in the lumbar and mesenteric lymph glands the right that vein was invaded by growth, and blood borne metastases were present in the lungs.

UTERINE TUMOURS CONTAINING BOTH EPITHFLIAL AND NON EPITHELIAL TISSUES

The lesion formerly spoken of as 'adeno myoma' is no longer regarded as a neoplasm but as a hyperplastic extension of the endometrium into the myo metrium accompanied by hypertrophy or hyperplasia of the muscle-adenomyosis or endometriosis interna However, true tumours containing both epithelial and muscular neoplastic tissues do occasionally occur, for both components may reappear in metastases Thus Hart reported the case of a woman aged 72 who had had a large uterine tumour removed 22 years previously, and who was found at necropsy to have multiple small well defined tumours in the lungs, careful search failed to discover any other primary growth, and microscopically



(x 120)Fig 258 -Case III Pulmonary metastasis with structure of adeno myoma

the pulmonary nodules presented the typical structure of fully differentiated "adeno myoma" with glandular acini and small cysts embedded in smooth muscular tissue. The following personally studied case was similar to Hart's, except that the primary growth in the uterus had become sarcomatous

Case III - History-A woman aged 58 underwent subtotal hysterectomy for fibroids the tumours were not examined miscroscopically. The patient returned to hospital 3 months later with a large recurrent tumour in the pelvis and died 2 months after this Necrops: -A large necrotic growth filled the pelvis and there were scattered metastases in the peritoneum and in the iliac lymph glands from which the tumour had invaded the inferior vena cava The lungs contained a few small firm white well defined spherical nodules Histology—Many parts of the pelvic growth and its peritoneal metastases were examined and all showed anaplastic spindle celled sarcoma devoid of epithelial elements The lung nodules (Fig 258) showed well differentiated epithelial acini lined by cubical or low columnar cells set in abundant smooth muscular and fibrous tissue

(1) Frequency

Norns s paper tabulates many reported series of cases of cervical carcinoma totalling 9 509 cases of which 542 (i.e. 57 per cent) were adenocarcinomas. The percentage in different series however differed greatly from 1 6 to 117 owing no doubt to the uncertain limits of the group. Griffin found 94 of 749 cervical carcinomas (12 6 per cent) to be of glandular type.

(2) Age

The average age of Norris s 43 cases was 47 two thirds of them were in the fifth and sixth decades and the youngest was 28 Cullen also found the disease to occur most often between the ages of 45 and 50 years

(3) Marital state

Of 13 of Cullen's cases 12 were married and had borne children. Of Norris's 43 patients 38 were married or widowed and 80 per cent had been pregnant or had had operations on the cervix. Unlike endometrial adenocarcinoma there is no evidence that sterility predisposes to cervical adenocarcinoma.

(4) Macroscopic appearance

This varies widely the tumours may be ulcerated papillary nodular or diffusely infiltrating and they may arise in the vaginal part of the cervix within the cervical canal or intramurally

(5) Microscopic structure

Norns s many excellent figures sufficiently show the wide range of structure and the impossibility of making any useful sub division of the group Tumours of imiglied epidermoid and glandular structure adeno acanthomas are rare Mueus secretion by the tumour cells also appears to be infrequent but when it is present it affords the most substantial evidence of the genuinely cervical origin of the tumour Elsewhere (1931) I have recorded an example of well differentiated mucoid adenocarcinoma of the cervix and Griffin described two cases of this kind. Cullen described an unusual case of mucoid adenocarcinoma widely involving both cervix and corpus with great enlargement of the uterus

(6) Growth and metastasis

In behaviour and prognosis the tumours more closely resemble cervical epidermoid carcinoma than endometrial adenocarcinoma. In many cases there is early infiltration of the cervix spread to the parametria and metastasis to regional lymph glands. However again the uncertain limits of the group make it futile to attempt to generalize about its behaviour or to calculate the frequency of metistasis. In the only case of undoubted cervical adenocarcinoma on which I performed necropsy referred to above the large growth had directly invaded the appendix and ileum, there were metastases in the lumbar and mesenteric humph glands the right iliae vern was invaded by growth and blood borne metastases were present in the lumps.

examination-The uterine cavity was distended by a mass of firm papillary and finely cystic growth 5 centimetres in main diameter which sprang by a broad base from the fundus replacing almost the whole of the endometrium of the upper two thirds of the organ. The growth was well demarcated from the uterine muscle which though thicker than normal was unaffected Histology (Fig 259)-The growth had a coarsely papillary structure the papillae being clothed by endometrial epithelium and containing many multiplying glandular acini and cysts. The stromal tissue was everywhere abundant and cellular consisting partly of undifferentiated compact spindle-celled growth partly of less compact stellate celled growth like mucoid embryonic tissue and partly of differentiating bundles of smooth muscle fibres with all transitions between them mitoses were fairly numerous areas of majure fibrous and myomatous tissue also were present

In this case the bulky tumour clearly had a purely endometrial origin. The epithelial acini and eysts were endometrial, and the intervening undifferentiated and smooth muscular tissue occupied the place of a greatly overgrown endometrial stroma and had no demonstrable connexion with the myometrium. The neo plastic muscle was developing by metaplastic transformation of the undiffer entiated stroma. Such a transformation loses something of its novelty when we come to study the purely mesenchymal mixed tumours of the uterus, which also arise in the endometrium, and in which as we shall see later, striated muscle, cartilage bone, adipose and mucoid connective tissue all appear

It is possible then that the tumour of Case IV affords a connecting link between the true adeno myomas and the non epithelial mixed tumours of the uterus It may be that an adeno myoma-or its malignant counterpart-is of purely endo metrial origin and is that particular variety of mixed tumour which is composed of neoplastic endometrial epithelium and neoplastic smooth muscular tissue, the differentiation of the latter from the plastic stroma perhaps being determined by the very presence of the former Nicholson (1918) described a remarkable specimen of multiple mixed lumours of the endometrium in which the non epithelial components comprised mucoid tissue, eartilage adipose tissue and musele and the epithelial component was cancerous and appeared along with the non epithelial tissues in metastases Those endometrial mixed tumours which contain no neoplastic epithelium but are composed of a variety of mesenchymal derivatives are described further in Chapter 48

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Comment—Evidently sarcomatous change had occurred in a uterine adeno myoma which had already produced small metastases of benign mixed type in the lungs

We might reasonably assume that in such tumours the muscular component has arisen from the myometrium. But that this is not necessarily so is shown by

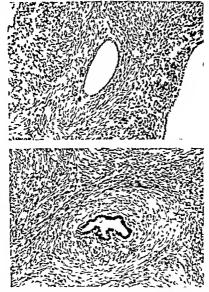


Fig. 259—Case II — Endometrial mixed tumour containing epithelium lined spaces separated by cellular stromal tissue with abundant differentiating smooth muscle — (× 120)

the following unusual case in which a mixed tumour containing both epithelial and muscular tissue seems clearly to have come from the endometrium alone

Case II (Dr. D. M. Seele, s case)—History—A woman aged 70 had noticed dysuma for 3 months and examination showed that this was due to firm incarceration of a greatly enlarged uterus in the pelvis. She had had 3 children uncentfully no miscarriages, a normal menstrual history and an uncentfull menopause. During operative removal of the uterus it was noted that the ovaries tubes and persioneum were normal. hakelege

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its first digital removal, but did not recur after its second removal by superficial curetting. Secondary growths in the vaginal walls, especially from primary carcinomas of the uterus or of the kidney (q v), must not be mistaken for primary adenocarcinomas of the vagina.

Primary melanomas of the vagina are described in Chapter 58

(7) Metastases

From carcinoma of the vaginal outlet these appear first in the inguinal lymph glands but more cranially situated growths metastasize mainly to the pelvic and lower lumbar elands

(8) Vaginal carcinoma in animals

This disease is not uncommon in horses and cattle, and is seen occasionally in dogs (Feldman)

CARCINOMA OF THE VULVA

In their structure and behaviour, the epithelial tumours of the vulva resemble those of the skin in general, but with certain special features By far the commonest form of growth is invasive squamous cell carcinoma, much less frequent are basal cell growths, Bowen's disease, and tumours of sweat or apocrine glands and of Bartholin's glands, which we will consider separately

(1) Frequency

Carcinoma of the vulva is commoner than carcinoma of the vagina, but is yet a relatively rare disease. Graves and Mezer saw only 66 cases while they saw 1,668 cases of carcinoma of the cervix and 475 of the body of the uterus Rentschler estimated the disease to occur once to every 25 cases of cervical carcinoma.

(2) Age

About half of the patients are over 60 and about one third of them are in the seventh decade. The mean age in Taussig's series was 58 and in Graves and Mezer's 60 years. Patients under 35 years of age are rare

(3) Marital state and parity

Of 154 of Taussig s patients, 101 had borne children 42 were nulliparous and 11 were virgin Of Rentschler s 71 cases, 11 were nulliparous

(4) Site

The epidermis is more frequently the site of growth than the vestibular mucous membrane. In Taussig s series 104 tumours were epidermal 11 vestibular, 12 peri urethral, and 2 from the glans of the clitoris, while 12 arose in Bartholin s glands. Graves and Mezer classified the primary sites in their cases as labial in 39, peri urethral in 9, in the region of the clitoris in 10, perineal in 2, and in

CHAPTER 32

EPITHELIAL TUMOURS OF THE VAGINA AND VULVA

CARCINOMA OF THE VAGINA

(1) Frequency

CARCINOMA of the vagina is a rare disease comprising only about 1 per cent of action mass of the female gental tract. In Moench's series its frequency relative to action mass of the cervity was 1 to 43.

(2) Age

The mean age of Moench's 59 cases was 49 years and of Emmert's 37 cases 53 years and their youngest patients were 28 and 26 years respectively. Hoge and Benn reported a vaginal tumour in an infant of 5 months fatal at the age of 3, but their microphotograph does not support their diagnosis of 'adenocarein oma and the nature of the tumour remains uncertain

(3) Marital state and parity

The number of proved recorded cases is too small to permit eorrelation of the frequency of the disease with the reproductive history Moeneh's series included 36 married and 5 single women 7 of Emmert s 37 patients were nulliparous

(4) Site

More than one half of the recorded tumours have arisen on the posterior vaginal wall. Emmert stated that in 13 of his 37 cases the growths were multiple but he gave no details

(5) Pre-eancerous lesions

No definite predisposing lesions have been recognized

(6) Structure

With rare exceptions the tumours are squamous cell careinomas of varying degrees of anaplasia. Of Moench's 37 microscopically examined tumours 35 were squamous celled and 2 were adenocarcinomatous, and the corresponding figures in Emmert's series were 29 and 1. Remains of Gartner's duct and endometriosis of the recto vaginal septium have both been suggested as possible origins of adenocarcinomas. Meyer (1907) was the first to describe a papillary carcinoma of Gartner's duct in the vulit of the vagina and Nicholson depicted a similar growth. Strachan recorded 2 cyses of adenocarcinoma of papillary type and referred to other reported instances. Spencer reported a rumark able large frable adeno papillary growth attached to the vaginal fornix by a narrow pedicle. This was removed digitally and had not recurred 24 years later. I have studied a very similar frable pedineutilated growth superficially attached to the upper posterior vaginal wall in a spinister of 68 years. This recurred after

- (a) Epidermoid carcinoma, of the usual invasive type, and usually cornifying, is by far the commonest
- (b) Intra epidermal carcinoma or Bowen's disease, non invasive for long periods, is sometimes seen (Knight, Jeffcoate et al) Occasionally, as in the case depicted in Figs 262 and 263, examination of the vulval tissue removed for leucoplakia shows also the changes of Bowen's disease Two of Knight's 6 patients with Bowen's disease had leucoplakic changes as well
- (c) Basal cell carcinoma is rare (Wilson)



Fig 265 - Hydradenoma of vulva from a woman of 32 years (× 60)

(8) Metastasis

The inguinal lymph glands may be involved early, and are estimated by Taussig to become affected during the course of the disease in about two thirds of the cases Inflammatory swelling of the glands may, however, be mistaken for metastases, and microscopical examination of all excised glands is important for prognosis Remote metastases have rarely been reported

(9) Vulval careinoma in animals

This occurs in horses, cattle and dogs Rudduck and I studied a squamous cell carcinoma of the perineum in a 5 year old eow and a recurrent multiple squamous cell carcinoma of the labium of a 14 year old white mare

TUMOURS OF THE VULVAL GLANDS

(1) Tumour of Bartholin's glands

These comprise well-circumscribed benign adenomas, usually cystic and mucus secreting and invasive carcinomas, usually glandular but sometimes

Bartholm's gland in one case Caremoma supervening on leucoplakia often appears at multiple sites (see below)

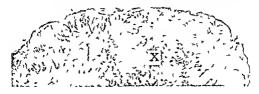
(5) Pre-cancerous lesions

Pre cancerous lesions are present in a high proportion of cases. The commonest of these is the chronic form of vulval dermatitis variously designated 'leuco plakia', "leucoplakic vulvitis", kraurosis' and scleroderma circumscripta'



Fig. 260—Early superficial carcinoma from near chitoris in a woman aged 65. Arrows show the limits of the cancerous area as revealed microscopically. (× 21)

(Taussig, Adair and Davis, Ketron and Ellis) I agree with these writers that these names do not refer to distinct diseases but merely to different appearances or stages of one disease and that this is a dangerous pre cancerous condition. Microscopic evidence of it was present in the majority of specimens of vulsal cateinoma which I have examined Of Taussigs 107 microscopically verified.



Fio 261 —Extensive superficial labul careinoma from a woman aged 60 consisting mainly of short downgrowths from the still intact epidetims. At X there is a more deeply penetrating mass of growth. (x 8)

cases of epidermoid cateinoma leucoplakin was present in 74 i.e. 69 per cent in Graves and Mezer's series the percentage was 55. Taussig estimated that one third of patients with leucoplakia will develop carcinoma while Adair and Davis considered that more than one half of them will do so. In leucoplakie

- (a) Epidermoid carcinoma, of the usual invasive type, and usually cornifying, is by far the commonest
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TUMOURS OF THE VULVAL GLANDS

(1) Tumours of Bartholin's glands

These comprise well circumscribed benign adenomas, usually cystic and mucus secreting and invasive caremomas usually glandular but sometimes squamous celled in structure The following case affords an example of the former

Case I—History—A woman of 60 had had a cyst of the vulva for many years This occupied the position of Bartholins gland and when enucleated it proved to be a well defined growth 4 centimetres in diameter composed of some solid tissue and multiple small cysts containing mucus. Histology (Fig. 264)—The cysts were lined by cubical or columnar epithelium partly mocus secreting and in places multilayered and papillary Other parts showed cribinform structure closely resembling that seen in mammary and salivary tumours or more disorderly adenocarcinoma like structure. The stroma and capsule were densely fibrous and partly hydine.

Simendinger tabulated 38 recorded cases of carcinoma of Bartholin's glands Most of these were adenocarcinomas, but others including Simendinger's case were epidermoid carcinomas. Probably no sharp separation should be made between the two types of growth, nor between these and benign tumours of somewhat atypical structure like that just described. Simendinger's review afforded no conclusive evidence that infection of Bartholin's glands predisposed them to tumour formation.

(2) Tumours of sweat and apocrate glands

account of 155 cases)
Taussig I J (1941) Cancer Res 1 901
Wilson J M (1941) Arch Surg 43 101

These do not differ from those of other parts of the skin (see Chapter 14) The vulva is one of the commonest sites of benign hydridenoma (see Danforth, Gardner and Fig 265) and locally malignant growths of the same kind also occasionally occur here (McDonald)

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CHAPTER 33

EPITHELIAL AND RELATED TUMOURS OF THE TESTIS AND EPIDIDYMIS

INTRODUCTION

It would be of little use to recount the confused views which were held of the nature of testicular tumours during the later part of last century when sarcomas and "endothelomas" abounded and when many teratomas were called chondromas" chondro carcinomas", 'rhabdo myomas , "myo chondromas', etc., according to the tissues which had been detected in them Amongst the first to clarify the confusion were Chevassu (1906) and Nicholson (1907) Chevassu's admirable monograph clearly described and distinguished the two common forms of testicular growth, teratoma and seminoma, maintaining that the latter was carcinoma of the seminal epithelium ("epitheliuma seminal"), and described also interstitula cell tumour and testicular adenoma Nicholson independently showed that testicular sarcomas were relatively rare and seminal carcinomas common and that teratomas formed a single group of variable structure.

In 1911, Ewing finding seminoma or seminoma-like tissue in some teratomas, advanced the view that seminomas, or as he called them, "embryonal carcinomas", did not arise from the seminal epithelium but from teratomatous precursors, they were he said, one-sided developments of teratoma." Ewing s view, maintained up to the last edition of his book in 1940 and still widely accepted, has caused great confusion in the classification and analysis of the properties of testicular tumours. Embryonal carcinoma. became, for many writers, a dumping ground for all cellular malignant growths, seminomas and teratomas alike.

Because malignant teratomas and seminomas do not differ greatly in their prognosis and treatment, clinicians found little disadvantage in this confusion of the two groups. But pathologists interested in the fundamental problems of histogenesis, found themselves in a dilemma. On the one hand, from the work of Chevassu, Nicholson, Dew, Bell, Deitermann and others it seemed clear that the origin of seminomas was from the spermatic epithelum. On the other hand the undoubted coexistence of seminoma with teratoma in some cases and studies of the horimonal results of the various testicular tumours, lent plausibility to Ewing's view and gave it wide popularity. Some writers e.g. Cairis, Innes, Harvey and Dawson attempted to reconcile the two conflicting views by assuming that primitive totipotent germinal cells in the seminal epithelium are the source of both seminomas and teratomas. This assumption is not very satisfying

Some years ago, hoping to settle this difficulty to my own satisfaction I began to collect testicular tumours and study them as fully as the available material permitted. This material, on which the conclusions reached in this chapter are

largely based, was the following

commonwelled in contains. The following one affords an entire of the ferne

כביר ו-ברידי-ל שומבים פי ול לבול לביל פי "מים" פו לביר דולים מי בינים ייצוב This commend the prestore of Barberra's giral and when employed; proved a be a and an interest if a core a income manual in manufam - it con including and one commerce was Her ber (Fig. 14)-The one was look by coing. פי מוליותים מינוליות, וינול מינוש יינוליות במל מו ולניים מינוליים ליל ועול ביל ועול ביל בים ביורים לו המולים לו מורים לבי לו מורים לבי לו מורים לבי לבי לבי לו המולים לו המולים לו המולים לו המולים לי Capture were deasely filtrous and partly hyaline

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Cancer of the vulva Amer J Obst Gin 40 764 (A useful account of 155 cases)

Taussig F J (1941) Cancer Res 1 901 Wilson J M (1941) Arch Surg 43 101 and my own series respectively. The disease is rare before the age of 30 and almost unknown under 20 years. Bell (1938) his recorded the development of seminoma in a boy of 16 years with bilateral incomplete descent of the testes. The findings in my youngest patient are worthy of special note.

Case I —History—A married man aged 27 years, father of 3 children had both tester in the inguinal position—the right testis by in the inguinal canal and could not be drawn into the section—the left testis—which felt abnormally firm and nodular lay at the external ring and was accompanied by an easily reducible inguinal herma—Left orchidectomy



Fig 266 - Case 1 Large lymphoid follicle in stroma of seminoma (x 60)

and repair of the herma were performed. Examination of the testis showed it to measure $4.5 \times 3 \times 3$ centimetres and serial that shees showed it to contain at least 6 separate areas of white growth separated by testicular tissue. this was verified in micro-sections of the entire orgin. Histolog—Typical seminoma with unusually abundant lymphoid tissue in many places bulker than the seminomatous tissue and forming many large follicles with germinal centres (Fig. 266). No teratomatous elements were found in any of the growths. Intervening testicular tissue showed extreme tubular attrophy and fibrosis and many large groups of interstining cells.

(b) The duration of tumours

This is very variable. In some cases they grow and disseminate quickly in others enlargement of the tests has been noticed for 5 or 10 years or longer prior to removal (references by Gordon Taylor and Till). Removal of some of these slowly growing tumours of long duration has been followed by permanent recovery, but the prognosis is bad in cases in which a previously slow growth has shown more rapid recent enlargement.

(c) Incomplete descent of the testis

This has long been recognized as predisposing to the development of tumours both seminomas and teratomas (Rea Gordon Taylor, Gilbert and Hamilton

| From | |
|------|--|
| | |

| | T . 1 | | | | EΛ | |
|---|---|---|---|---|----|-------|
| | Interstitial cell tumour | - | - | - | 1 | |
| | Multiple tubular adenomas of testis | - | - | - | 1 | , |
| | Probable rete carcinomas | _ | - | - | 2 | , |
| | ' Chorion epithelioma | - | - | - | 4 | , |
| | Combined seminoma and teratoma | - | - | - | 5 | , |
| | Teratoma of the epididymis only - | ~ | - | - | 1 | ,, |
| | Teratomas of the testis ~ | - | - | _ | 15 | , |
| | Tumours showing seminoma only - | - | - | ~ | 21 | cases |
| - | • | | | | | |

Total - - - 50 cases

From anmals

| Interstitual cell tumours in dogs - | | ~ | - | 16 cases |
|--------------------------------------|---|---|---|----------|
| Seminomas in dogs | - | - | - | 7, |
| Sertoli cell or rete tumours in dogs | - | - | - | 4 ,, |
| Teratomas of the testis in horses - | - | ~ | - | 5, |
| | | | | |

Total - - - 32 cases

All of the human specimens all of the equine teratomas, and most of the other animal specimens were very fully studied microscopically usually by many block from thin serial slabs of the tumours with the deliberate intention of discovering all available evidence regarding histogenesis and especially regarding the possible relationships of seminoma and teratoma. In many of the human specimens including all 5 of combined seminoma and teratoma complete topographical reconstruction of the growths was attempted in the manner indicated in my paper on teratomas in 1935.

It may be as well to state at once my main conclusions namely (a) that seminoma undoubtedly arises from the seminiferous epithelium and not from teratomatous elements (b) that cellular undifferentiated teratomatous epithelium has often been mis identified as seminoma or embryonal carcinoma (c) that the occasional combination of true seminoma with teratoma results from coex stence which though not due to histo genetic relationship is not wholly fortuitous and (d) that chorion epithelioma' is not a distinctive type of growth and is not chorionic but its only a form assumed by haemorrhagen necrotic cellular tumours of other kinds usually teratomas

SEMINOMA SEMINAL CARCINOMA OR SPERMATOCYTOMA

(1) Incidence and causation

(a) Age incidence

All adequate series from Chevassu's onwards show that true seminomas appear on an average more than a decade later than teratomas. The mean age of patients at the time of operation is early in the fifth decade e.g. 43, 45, 40, 40, and 43 years in Nicholson's Bell's Deitermann's Gordon Taylor and Till's doctor On palpation doctor thought there might be a small nodular area in testis and because of this and patient's anxiety he performed orchidectomy. Incision of testis verified presence of a small well defined rounded slightly lobulated white tumour in upper pole. Histology.—Serial sections of the tumour showed it to be 9 millimetres in main diameter and to consist throughout of typical seminoma with no sign of teratomatous elements.

(e) Trauma

Injury has often been blamed as a cause of seminomas and other testicular growths but from critical study of cases in which this is supposed to have happened it is clear that in most instances the trauma did no more than attract attention to a testis already diseased, possibly aggravating it in some

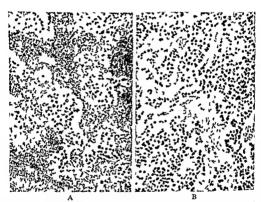


Fig. 267—Typical appearances of seminoma as seen in formalin fixed paraffin embedded tissue. A with abundant. B with scanty lymphoid strona. (x 120)

(h) Infections

Infections of the testis also are of very doubtful causative significance. Tuber culous epididymo-orchitis has occasionally been reported as accompanying testicular tumours (e.g. in 3 of Rea s cases), and of course a history of previous mumps is given by a proportion of the natients

(2) Structure

(a) The characteristic structure

Most, seminomas are closely similar to one another in structure and are easy to recognize at a glance and each tumour usually shows remarkable structural

and see also Bell's case and my Case I above) According to Gilbert and Hamilton ectopia is present in 11 per cent of cases of testicular tumour, a proportion 48 times greater than can be accounted for by chance if a tumour develops in a patient with unilateral ectopia, it is in the ectopic organ in almost all cases, and in men with bilateral ectopia if one testis becomes cancerous, then the other testis will also become cancerous in 25 per cent of cases, a risk 32 times greater than obtains in patients with scrotal testes. Ectopia is not necessarily the direct cause of tumour formation it is more probable that it is only one expression of gonadal or more general endocrine anomaly predisposing to tumour formation in the gonadal tissues.

(d) Bilateral seminomas

Bilateral growths are seen occasionally (Peirson Hamilton and Gilbert). The two testes may suffer nearly simultaneously as in Peirson's case or a period of many months or years may intervene between the appearance of the two tumours. Hamilton and Gilbert from a review of the literature, concluded that in a man with testicular cancer the likelihood of cancer arising in the second testis is hundreds of times greater than the chance expectation and that the risk is greatest in patients with imperfect descent. Teratomas as well as seminomas may be bilateral.

(e) Multiple seminomas in one testis

Multiple growths in one testis as in my Case I are seldom demonstrable in human specimens, but are frequently seen in dogs (see below)

(f) Familial incidence

Testicular tumours including seminomas have occasionally been seen in two or more close relatives. Champlin described the occurrence of testicular tumours in identical twins one died at 24 years of age of a testicular sareomy with intracramal metastases and at the age of 31 years the other developed a seminoma which was removed and had not recurred 3 years later. Raven reported a seminoma in a man of 38, whose brother had had an inoperable desicular tumour (not examined microscopically) at the age of 18. Lownes and Leberman described two brothers one of whom had a spermatocytoma removed at the age of 32 years but died later from pulmonary metastases and the other had a testicular teratoma removed at the age of 53 years, the photographs are poor and the nature of the second tumour is uncertain. The following case was remarkable not only for the family history of testicular disease but also for the small size of the tumour.

Case II (Dr. G. C. Burston's case)—Family, history—Palemal grandfather died at the age of 30 years from bilateral uterated cancer. of the testics father was killed in an accident and had no known disease of the testes—elder brother at age of 31 developed tumour of testis diagnosed by a pathologist as teratoma melastases in retroperationeal hymph glands and liver were seen at laparotioniny and he died later. Patient's history—When aged 15 he was operated on for undescended right testis—this was successfully placed in scrotum but remained only about half normal size. Al age of 38 he developed aching prain in groun became apprehensive because of family history and consulted his

in the tubules (Fig 268) This relationship has been interpreted by Ewing and others as due merely to tumour invasion of, and extension within, the tubules The appearances seen, however, cannot be explained in this way, but point clearly to progressive neoplastic change in the seminal epithelium. The seminomas of dogs (see below) often show transitions from normal to neoplastic tissue in the syspermatic tubules, and afford particularly conclusive evidence of the true origin of these tumours.

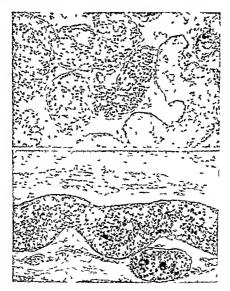


Fig. 268 —Intra tubular growth around the margins of a large seminoma (× 80)

(3) Are teratomatous tissues found in seminomas?

Keeping for separate consideration those tumours in which the coexistence of seminoma and teratoma is plain to the naked eye or on cursory microscopical study, we are left with those common seminomas in which on gross examination the tumour tissue appears of more or less uniform structure throughout and preliminary representative micro sections show seminoma only if Ewing s view

uniformity in all parts, save where this is altered by degenerative changes. The characteristic appearances are depicted in Figs 267 273 278 and 280. The tumours consist of well or ill defined clumps of large rounded polyhedral cells of average diameter about 15 or 20μ but sometimes even 30μ or more, with distinct cell boundaries each with a single large spherical nucleus and a rim of pale poorly staming cytoplasm devoid of any distinctive structures. The close similarity of the cells to spermatocytes in many tumours noted particularly by Bell is sometimes very striking and in itself points strongly to the spermatic origin of the growths. Mitotic figures vary greatly in number, according to the rate of growth of the tumours in rapidly growing tumours they are often very plentiful and conspicuous

In a personal communication Dr Leila Hawksley has drawn my attention to the great differences in appearance of the cells of seminomas according to the fixative used. The plump spherical shape of the cells is much better preserved by Bouin a Orth s or Zenker a fluid than by plain formalin or formalin solutions in which shrinkage and distortion often take place. Dr Hawksley also informs me that alcobol fixed seminoma cells show a high glycogen content

The stroma consists of strands of connective tissue and blood vessels characteristically accompanied by a variable number of lymphocytes. These may be scarty and found in only parts of the tumour, or they may be very numerous forming broad lymphoid areas alternating with masses of tumour cells Rarely this lymphoid tissue is as abundant as the tumour parenchyma and forms plentiful large follicles as well as diffuse areas as in Case I. The relative proportions of tumour parenchyma and lymphoid stroma though varying greatly from tumour to tumour are usually fairly constant throughout each tumour. Oedema of the stroma is sometimes prominent.

(b) Less usual structural variants

These are of three main kinds (i) Parts of the tumours sometimes show compact masses of large irregularly polygonal or elongated cells with denser cytoplasm giving more distinctly epithelial appearances. Growths in which this type of structure is prominent have often been designated carcinomas a distinct from seminomas but more complete study will show that the distinction is not valid for one tumour may contain areas of both structural types with transitions between them (ii) Diffuse anaplastic seminomas are occasionally difficult to recognize histologically and may be mistaken for sarcomas (iii) Near areas of necrosis or haemorrhage seminoma cells may become atypical showing enlargement and fusion. Rarely miltinucleated masses resembling the syncytum of the so called chorion epitheliomas may be produced in this way

(c) Relationships to the seminal tubules

In specimens in which residual testicular tissue is still present the relationship of the growth to this is often of great interest. I can abundantly confirm the findings of Hartmann et al. Bell and others that individual seminal tubules occupied by tumour are often to be found marginal to the main growths and that all transitions can be traced between normal spermatic tissue and tumour tissue.

(4) Extension and metastasis of seminomas

(a) Extra testicular extensian

Direct spread to the epididwnis and cord is frequent. Discrete nodules of growth may appear along the cord above the main growth, presumably by local embolic spread in veins or lymphatics. Extension to the skin, ulceration and fungation are of course seldom seen nowadays.



Fig 269 -Intra tubular multifocal seminoma in a fox terrier aged 14 years (x 40)

(b) Metastasis ta lymph glands

This is the major risk. The first glands to be affected are those of the upper lumbar groups, about the level of origin of the spermatic arteries. In a high proportion of fatal cases tumour deposits are present here, and in deciding on operability of a testicular tumour, and in the follow up of patients already operated on, careful palpation for possible retroperatoneal metastases is the most important part of the clinical examination. Other lymph glands become involved secondarily to the disease in the lumbar group or following extension of inoperable growths to surrounding tissues.

(c) Metastasis by the blood stream

Haemic dissemination occurs later and less frequently from seminoma than from malignant teratoma. The prognosis of seminoma is correspondingly better than that of teratoma, and as Gordon-Taylor and Till have rightly insisted, far too pel simistic an outlook has prevailed regarding testicular neoplasms. Since

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were correct, we should certainly expect that thorough serial study of these tumours especially small ones would often reveal residues of the teratomas from which they are supposed to have sprung. But such residues are not found in the ordinary seminomas. Bell Dentermann and Innes et al. all failed to discover any signs of heterotopic tissues in their seminomas. In my own series of 21 seminomas. I deliberately searched for such tissues with special thorough ness usually in many sections from tim serial slubs of the entire tumours but found no sign of teratomatous elements.

Ewing admitted that teratomatous elements could not be found in most seminomas but supposed this to be due to complete suppression of slowly growing and scanty structures in the original focus. Yet grossly obvious specimens of combined seminoma and teratoma are not unusual (see below) and if these are taken to support Ewing 8 hypothesis we should surely discover even more frequent microscopic examples of the combination. This however is not the case, and this very discrepancy argues strongly against the hypothesis.

Again Ewing's assertion that scanty teratomatous elements are soon over grown and destroyed by the rapidly advancing carennoma is very dubious on the contrary study of malignant teratomas shows plainly that islands of cartilage squamous epithelial cysts and other well differentiated structures are not readily overgrown and destroyed by more malignant anaplastic components of the growths and moreover many seminomas are not rapidly advancing destrictive tumours.

Eving s Case I on which he largely based his concept of obliteration of the gatesmannian stream of the result to this question. The tumour showed two rather distinct portions one of which proved to be seminoma and the other teratoma the latter being sharply circum seribed from the testis. Thus teratomatous part was progressing rapidly by the growth of several types of carcinoma and capable of yielding esentially one of the pure types of carcinoma testis. If this tumor had been allowed to grow to the size of a line seg it would have been regarded as adenocared noma or chorioma in one portion and diffuse carcinoma or alreolar sarcoma in the others. This is pure assumption. All that the tumour actually showed was two rather distinct portions one seminomatous the other teratomatous.

The occasional presence of small islands of cartilage in seminomas has often been cited in support of Ewing's hypothesis. The only recorded instruce of this which I have rend is that of Leroux and Huffagel who found associated with a seminoma in area of cystic tubules and some nodules of cartilage. These were interpreted not as teratomatous but as due to obstructive dilutation of the excretory duets of the testis and metaplastic chondification of the stroma

Briefly then the facts are these. The ordinary seminoma of grossly homogeneous in-ked eye appearance, has a homogeneous microscopic structure—and thorough sterial examination—even of small or slowly growing tumours shows no signs of teratomatous tissues. The concept of submergence and obliteration of a pre-existing teratoma by seminomatous growth lacks substantial evidence and is wholly imaginary. tumour No II, on which he laid such stress, was 9 centimetres in diameter and that it was not examined topographically

Briefly then, embryonic epithelial growth in teratomas can be, and has been, mistaken for seminoma or embryonal carcinoma" (used synonymously for seminoma). But, this source of confusion can and should be avoided by careful study of the material. When, however, tissue structurally indistinguishable from seminoma is found in a teratoma, it may still be some teratomatous component merely mimicking seminoma, or it may be true seminoma invading the teratoma from without. These possibilities must always be carefully weighed before concluding that true seminoma has arisen within a teratoma.

Age meidence —In all adequate series of eases the mean age of patients with teratomas is about 10 years younger than that of patients with seminomas, e.g. 28 in Chevassus and in Gordon Taylor and Tills series and 32 in mine. A further striking difference is that, while seminoma rarely, if ever, occurs in child hood and adolescence, teratomas often do so and are sometimes known to have been present at birth. Thus, in Chevassu's series there were 5 specimens of teratoma from infants but no case of seminoma under 20 years of age. The fact that, although teratomas, some of them malignant, are not unusual in childhood and adolescence, seminomas are praetically unknown during this period strengthens the case against Ewing's hypothesis

Teratoma testis in animals —The only mammal I believe, in which testicular teratomas have been observed is the horse (Wilhs Rudduck and Wilhs, Innes) These tumours appear to be commoner than their human counterparts, are present in young animals, are usually benign and highly differentiated and may be multiple and bilateral Seminomas, which occur relatively rarely in the horse, are not associated with teratomas. The spontaneous and experimental testicular teratomas of birds are discussed in Chapter 61.

COEXISTENT SEMINOMA AND TERATOMA

(1) Previous reports

In addition to those tumours in which teratoma and seminoma or seminoma like growth have been found intimately associated, there are several reports of cases in which the two have coexisted as distinct and separate tumours or in which their relationships have been such as to suggest that they had originally been separate

Lecene (1907) briefly recorded a testicular tumour from a man 40 years of age which showed both teratoma and seminoma. No topographical study was made, but in many pieces examined the two forms of growth were everywhere separated by a zone of connective tissue and nowhere infiltrated one another. In a second specimen reported by Lecene (1909) the testis of a man of 25 years contained two quite separate growths one a seminoma and the other a cystic teratoma the latter encapsulated by a fibrous zone.

many semmomas grow slowly and metastasize late many permanent cures can be effected by prompt surgery Semmomatous metastases are commonest in the lungs and liver and are rare in other parts

(5) Semmomas in animals

Seminomas clearly the counterparts of those in man are very common in Innes and Huggins and Pazos with whose findings Rudduck s and mine on specimens from 7 dogs are in substantial agreement. Like human seminomas the canine ones are not infrequently bilateral and they appear to affect undescended testes with disproportionate frequency. Early timours are often demonstrably

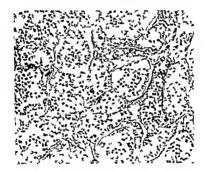
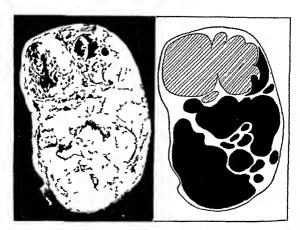


Fig. 270 Intra tubular seminoma in a Pomeranian dog aged 11 years (x 100)

multiple intra tubular seminoma in situ is often conspieuous (Figs. 269–270) and the progressive origin of the growths from spermatic cells of the seminal tubules is often clear and unmistakable. The careful study of a few good specimens of canine seminomas should soon convince any competent histopathologist both that these tumours are the same as human seminomas and that they arise from the spermatic epithelium—spermatogonia or spermatocytes. A still further point in evidence against the hypothesis that seminomas are of teratomatous origin is the friet that while canine seminomas are common teratomas of the dog s testis are extremely rare if indeed they ever occur—as far as I know there are no recorded examples. Crimie seminomas are much less malignant than their human counterparts growing slowly and rarely metastasizing. However, Fig. 271 depicts invasion of the tunica albuginea—and Rudduck and I saw also a large seminoma in an 8 year old setter with metastasses in the lumbar lymph glands and here.

(2) Personally studied cases

I have examined the following 5 cases in which seminoma and teratoma coexisted topographical study showing certainly or almost certainly that the two kinds of growth were distinct in 4 cases, and that they may originally have been distinct in the remaining case



F o 272—Case III A vertical section with key diagram showing seminoma black and teratoma hatched (Slightly reduced)

Case III (Mr H C Trumble s case) -History-A man of 23 years had noticed swelling of one testis for several months orchidectomy was performed retroperstoneal masses were noticed about I year later these diminished following X ray treatment, but later recurred and patient died 3 years later at age of 27 years Naked eye examination showed an ovoid lobulated growth 8 x 5 y 5 centimetres surrounded on most aspects by a compressed layer of residual testis. A series of thin vertical slices showed that the upper third of the tumour consisted of polycystic growth characteristic of teratoms and its lower two thirds of homogeneous solid white and partly necrotic growth on the mediastinal side the two areas had visible residual testis intervening between them but on the opposite side they were closely contiguous but still well demarcated. This demarcation was apparent in all slices, one of which is depicted in Fig 272 The slices were all cut into numbered blocks from which micro-sections were prepared Microscopical examination confirmed that the upper third of the tumour was malignant teratoma and the lower two-thirds typical seminoma. The teratomatous t ssue comprised a variety of well differentiated glandular structures disorderly adeno carcinoma like tissue keratinized nests of squamous stratified epithelium smooth mustle,

In Ewing's Case I already referred to the tests of a man of 38 years contained a tumour $2 \times 14 \times 1$ centimetres composed of two rather distinct portions one seminomations and the other which was sharply circumstribed from the testis teratomatous and containing choriomatous elements. In Ewing's Case II the tumour from a man of 61 years included both a highly differentiated teratomatous growth and a large area of seminoma. The latter judging from Ewing's diagram enveloped the former peripherally but was fairly distinct from it but no details are given regarding the exact relationships of the two kinds of growth.

A brief note records that Menetrier et al saw two tumours in the one testis a seminoma and a chorioma separated by testicular tissue

Another specimen of coexisting but distinct seminoma and teratoma in a man of 36 years was fully described by Hartmanne tal. The seminoma, typical in structure and showing clear evidence of its derivation from the testicular tubules occupied the upper pole of the testis. A chorioma occupied the mediastinal area and epididymis and was separated from the seminoma by a zone of connective tissue. It showed typical chorion-epitheliomations structure but with transitions to papillary epithelial formations. The authors regarded the seminoma as having arisen in the testis independently of but consecutive to a pre existing embryoma, the latter becoming predominantly choriomatous.

Roussy and Huguenin described a tumour from a man of 20 years one area of the growth was typical seminoma and another was a teratoma with cysts and papillary tubular epithelial structures regarded as Wolffan No topographical details are given but the two parts of the growth were said to be distinct

McClure et al found in the testis of a man of 29 years a well delimited terationa separated from the surrounding testieular tissue by a thin but definite apsule of fibrous tissue along with an area of spermatocytoma in residual testicular tissue at the upper pole of the organ the appearances seen in further slices of the bisected testicle suggesting that the tumour passes as a band from the upper to the lower pole. The authors described the tumour is showing a seminoma in addition to the malignant teratoma.

Nicod reported a tumour from a man of 26 years in which both semino matous and earcinomatous parts were present infiltrating each other in places. Their topography was not fully determined but Nicod interpreted them as having been distinct tumours which had eoaleseed.

In the tertis of a man of 27 years McDonald and Broders found two distinct tumours which though in continuity in places were for the most part separated by normal testicular tissue or by a capsule one tumour was a teratoma and the other a seminoma. Detailed topographical study was not undertaken McDonald and Broders also mentioned a specimen reported by Mercier and Bourque in which three separate tumours—a teratoma a seminoma and a chorion-epithelioma—are said to have been present. Peyron reported having seen examples of coexisting seminoma and teratoma.

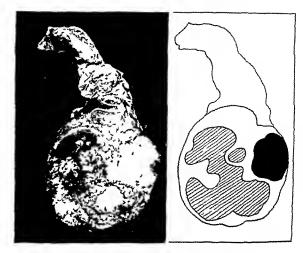
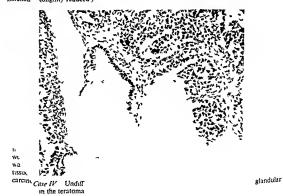


Fig. 274 — Case IV A vertical section with key diagram showing seminoma black and teratoma hatched (Slightly reduced)



and immature spindle-celled mesenchyme. The disorderly adenocarcinoma like epithelium was plentiful and in places formed irregular meshworks or diffuse sheets and its large polyhedral cells showed many minote figures. This fissure resembled that of Figz. 275 and 276 and bore a superficial resemblance to seminoma in places but closer study showed that it could everywhere be distinguished from the typical seminoma in the lower two thirds of the testis. Sections of the zone between the terationatous and seminomatous areas showed these to be well separated in most parts by a hand of residual testis and a thick fibrious layer but that on the outer side of the festis the two kinds of tumour became closely contiguous and a tongue of seminoma intervened between the outer aspect of the terationa and the tumou a fluginea. However no seminomatous issue was found within the limits of the teratomatous growth. Calcified spherules were present in residual attorbite seminal tubules included in the seminoma (Fig. 273).

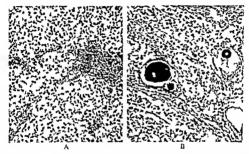


Fig. 273 —Case III Seminoma of typical structure in A with calcified intra tubular spherules in B (× 115)

Case IV-Hustors-A man of 28 years had noticed enlargement of left testis for orchidectomy was performed his final fate is not known. Naked eye examination showed a lobulated tumour 7 centimetres in main diameter surrounded by a zone of residual tests of maximal width I centimetre at the upper pole. One well-defined lobule of growth 2 centimetres in diameter in the mediastinal region consisted of homo geneous white tissue the remainder of motifed grey brown and harmorrhagic growth (Fig. 274) The whole tumour was cut into vertical slices and then into 26 numbered blocks from which micro-sections were prepared. Histolies (Figs. 275 and. 276)-The white lobule of growth had the typical structure of seminoria and was everywhere distinct from the teratomatous remainder though closely contiguous with it in part. The teratoma consisted largely of disorderly poorly differentiated adenocarcinoma like growth like that of Case III and of a small patch of better differentiated tissues comprising some small cysts lined by squamous stratified epithelium or by papillated columnar epithelium and glands of alimentary type accommanied by lymphoid tissue and cellular spindle-celled mesenchymal tissue. No seminomatous tissue was found within the teratoma some of the least differentiated parts of which however might have been mistaken for seminoma on superficial examination (Fig. 276)

later Naked eye examination—Testis measured 4 × 4 × 3 centimetres and was largely replaced by growth in its upper third his consisted of lobiles of homogeneous white itssue in its lower two-thirds of irregularly cystic tissue the two areas appearing fairly distinct (Fig. 277). Histology (Fig. 278)—The white area of growth is typical seminoma the cystic part is malignant teratoma containing cysts lined by gobiet-celled alimentary epithelium or by columnar or cuboidal epithelium of nondescript type comified cell inests and spaces lined by epidermis-like epithelium plentiful poorly differentiated papillary or retiform epithelial tissue smooth muscle around some of the cysts small nodules of cartilage and much cellular spindle-celled mesenchyme. Vertical sections at several different planes show that the two kinds of growth are everywhere separated by a thek zone of fibrous tissue except at one place (marked X in Fig. 2778) where the seminoma has slightly invaded the periphery of the teratoma over a small area.



Fig 278 - Case V A from seminoma B from teratoma (× 120)

Case VI - History - A man of 34 years had noticed swelling of right testis for 9 months orchidectomy was performed final result not known Naked eye examination-An ovoid tumour 14 x 9 x 8 centimetres was enclosed within the tanica albuginea with only a thin rim of compressed residual testis on outer surface. It was composed of mottled white and degenerated solid tissue with a few well defined small cysts near upper pole The whole tumour was cut into vertical slices and then into 64 numbered blocks from which micro-sections were prepared Histology-Most of the tumour is clearly teratomatous consisting of much disorderly adenocarcinoma like growth along with a variety of better differentiated glandular structures mainly of mucus recreting columnar-celled alimentary type cornified cell nests and scanty smooth muscle and small nodules of cartilage Extensive necrosis has taken place in many parts of the teratomatous tissues and near the necrotic areas the poorly differentiated epithelial tissue shows swelling and fusion of the cells to produce chorion-epithelioma like appearances At parts of the periphery there is a layer of typical seminoma measuring up to 1 centimetre in thickness in some places restricted to the peripheral zone of residual testis and distinctly eparate from the teratoma in other places mingled with it. Where seminoma mingles with the undifferentiated epithelial component of the teratoma it is difficult to distinguish them No seminomatous tissue is present in the central parts of the growth it is restricted to the periphery

Case V (from Dr Leila M Hawksley formerly pathologist to the Cancer Hospital London)—History—A man of 27 years had noticed rapid enlargement of left testis for 2 weeks orchidectomy was performed a patientle upper abdominal mass was treated by deep X ray irradiation and patient was well and no mass palpable formorths

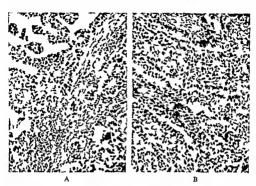


Fig. 276—Case IV Undifferentiated teratomatous epithelium in A accompanied by lymphocytes in B compressed and diffuse (× 110)

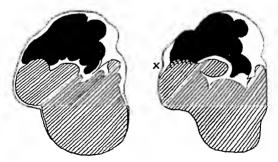


Fig. 277—Case 1 Key diagrams of two vertical sections showing seminoma in black and teratoma hatched (Actual size)

of benign structure, in all of the others the teratomas (or "chorion epitheliomas') were of the malignant type usual to the testis. The mean age of the cases, excluding these two, was 29 years, a figure identical with that for malignant testicular teratomas generally

I know of no example of associated seminoma and teratoma in an animal Seminomas are common in old dogs, but canine testicular teratomas are unknown Teratomas are rather common in horses, but seminomas are rather rare and have not been reported in association with the former

(4) Is the coexistence of seminoma and teratoma fortuitous?

In my opinion the facts enable us to answer no to this question. All testicular tumours are rare, and therefore the purely fortuitious coexistence of tumours of two distinct kinds in one testis would be excessively rare. Yet, as we have seen, the coexistence is not very unusual, and it would certainly be discovered more frequently if examination of excised testicular tumours were more thorough. The fact that no less than 5 cases of coexistence occurred in my series of 50 tumours most of which were unselected, indicates far more than a mere chance association.

In speculating on the relationship of the two growths, one fact seems clear the teratoma precedes the seminoma. This is evident, not only from the general principle that mammalian teratomas take origin in early stages of development (see Chapter 61), but also from the descriptions of the tumours in the cases just reviewed. In several of these (e.g. those of Lecene, McClure et al. McDonald and Broders, and my Case VII) the teratoma is described or depicted as a well circumscribed encapsulated mass and in others including Ewing's second case and my Case VII, the maturity of some or all of the teratomatous ussues points to their relative quiescence and long duration. The seminoma on the contrary is usually of the actively growing type with many mitoses and has often clearly been the component responsible for recent rapid enlargement of the tests. However while there is little doubt that the development of the seminoma follows on 'that of the teratoma and not vice versa it is also noteworthy that in many cases the teratomatous component also shows evidence of recent active growth and maltenancy.

What then is the possible relationship between a pre existing teratoma and a supervening but separate seminoma? Only a speculative answer can yet be given. We know that a developmentally abnormal testis such as an imperfectly descended one, is strongly predisposed to seminoma. Now, a testis containing a teratoma from early life is also a developmentally abnormal one. Perhaps, then it also for some similar but as vet undefined reason, is predisposed to later seminoma. Whether this hypothetical predisposition may be due to some primary disturbance of metabolism or endocrine control of the abnormal organ, or to diffusible products of the teratoma affecting the testicular tissues or merely to obstructive effects resulting from the mere presence of the teratoma, we cannot say. Whatever the explanation it at least seems clear that the coexistence of seminoma and teratoma in one testis is not purely fortuitous, but that a

Case VII (from Dr Leila M Hawksley formerly pathologist to the Cancer Hospital London) -History-A man aged 54 years had had enlarged right testis for 13 years growing larger during last 3 years orchidectomy was performed patient remained well 1 year later Gross structure—Testis and epididymis were both enlarged forming mass 6 centimetres in main diameter the testis contained a lobulated tumour 4 centimetres in diameter composed of white tissue with some areas of yellow necrosis, and the globus major of the epididymis contained a separate well defined growth 2.5 centimetres in diameter composed of masses of bone and cartilage cystic spaces and solid soft tissues Histology —Tumour in testis is a typical seminoma composed of unusually large cells with many mitoses, and showing many areas of necrosis near which the cells show giant and syncytial forms reminiscent of chorion epithelioma Abundant residual testicular tissue shows advanced tubular atrophy interstitual fibrosis and many large clumps of Tumour in epididymis is a well circumscribed encapsulated benign cystic teratoma composed of fully differentiated guiescent bone cartilage adipose tissue cysts lined partly by ciliated pseudo stratified conthelium and partly by simple cuboidal or flat enithelium abundant smooth muscle fibres around the cysts a few striated muscle fibres, and occasional natches of neuroglial tissue

(3) Discussion of foregoing cases

Of my 5 cases, the coexisting seminoma and teratoma were shown certainly to be distinct and separate growths in 2 (IV and VII) they had almost certainly been separate but showed close contiguity or very early localized infiltration in 2 cases (III and V) and they were not separate but showed extensive infiltration in Case VI In the 10 cases reviewed although detailed topographical studies were not undertaken it is either clear or very probable that the growths were distinct and separate in 5 namely those of Lecene (second case) Menetricr et al Hartmann et al McClure et al and McDonald and Broders the relationships are less certain but the tumours may well have been separate in 4 namely. Lecene's first case Ewing s two cases and Roussy and Huguenin s case while mutual infiltration was present in Nicod's case. Thus of the total 15 cases the tumours were either demonstrably separate or there was clear evidence that they had been separate in 9, in the two cases in which considerable infiltrative mingling of the two tissues was present (Nicod's and my Case VI) the distribution of the tissues suggested invasive coalescence of formerly distinct growths, and in the remaining 4 cases the relationships are uncertain. None of the cases showed what they should have shown if Ewing's hypothesis had been correct any evidence of histogenetic relationship between the teratomatous and seminomatous tissues

The ages of the 15 patients with combined tumours are noteworthy. They ranged from 20 to 61 years and averaged 33 years. Thus the combined tumours tend to occur about the same ages as malagnant teratomas of the testis and decidedly earlier than uncomplicated seminomis but like seminomas none of them has occurred in ehidhood or early adolescence. In the two oldest patients in the series—Ewing is second ease and my Case VII, aged 61 and 54 years respectively—the teratomatous growths were of highly differentiated benign type and I suggest that in both eases benign quiescent teratomas had long been present unnoticed until independent seminoma superviend. In Case VII the old benign teratoma in the epididymis was widely separated from the seminoma in the testis but in Ewing's case the seminoma soon enveloped the old teratomatous elements in the testis. These two eases are the only ones of the 15 with teratomas

tissue discovered is the well known cellular undifferentiated epithelium in its various forms—papillary, villous, syncytial, etc The structure produced may closely simulate that of true gestational chorion epithelioma, but so also may



Fic 280 -- Typical seminoma from a man of 45 years (x 80)



Fig. 281 —Chorion epithelioma like syncytial structure in the same tumour as Fig. 280 (× 80)

teratoma containing human testis is predisposed to the later development of seminoma in the remaining testicular tissue. When this happens, the teratoma often but not always, shows signs of active growth and malignancy also

CHORION EPITHELIOMA OF THE TESTIS

My series contains 4 tumours the haemorrhagic necrotic naked eye appearances and microscopical structure of which conformed with those of chorion epithelioma and in which no other definitely teratomatous elements were discovered (Fig. 279). In the better preserved areas of these growths however the supposed chorionic epithelium was identical with the undifferentiated papillary and reticular epithelial structures to which I have already referred as a frequent component of mahignant testicular teratoma (Figs. 275–276). Further, small haemorrhagic and necrotic foci in otherwise well preserved malignant teratomas



Fig. 279 - Chorion-epitheliuma of testis of a man of 22 years (× 80)

show an identical structure and the distinction between such teratomas and chorion epitheliomas is the purely arbitrary one of how much haemorrhagic necroite change the tumours show. The observations of Nicho'son Sternberg Schmeel Mönckeberg Reckendorf Handfield Jones Ahlstrom Ross McDonald and many others show how frequently chorion-epithelioma of the testis is demonstrably teratomatous. Many of these writers also have traced the relation ship of the chorion-epithelioma like tissue to other rapidly growing components of the teratomas. I agree with the following conclusion from the paper by Ross. The 'chorion-epitheliomatous tissue arises by the metamorphosis of undifferentiated cells which also give rise to careinoma and to teratomatous structures. These cells are in fact pluripotential.

A chorion-epithelioma is merely a rapidly growing teratoma in which liaemorrhage and necrosis are abundant and the predominant or only viable

later Necropsy—The testis was largely replaced by an ovoid slightly lobulated firm tumour 8 centimetres in diameter composed of white tissue with patchy vellow degeneration invading also the central part of the epididymis Lumbar lymph glands were much enlarged by masses of soft growth with gross invasion of inferior vera cava and left renal vein Cisterna chyli was invested and there were tumour deposits in left supraclaveurlar lymph glands. Lungs and liver contained many rounded metastases Histology—All parts of growths showed disorderly papillary adenocarcinoma (Fig 282) no areas like seminoma and no teratomatous tissues were found on extensive search of primary tumour

Case IX—A second specimen of unknown history consisted of a large pyriform growth 20 centimetres in vertical measurement invading the cord cranially and scrotal skin over its lower pole. Its structure throughout was similar to that of Case VIII but showed also the metaplastic formation of plentiful pale squamous cells from parts of the papillary erowth.

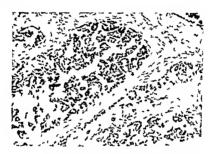


Fig 282 -Case VIII Papillary carcinoma of rete testis (> 80)

The unusual multiple tumours in the following case are of interest, because they appear clearly to have arisen from the excretory ducts, and because they bear on the histogenesis of the multiple testicular adenomas

Case λ —History.—A man 59 years of age, believed to have prostatic carcinoma (not proved microscopically) was treated by stilboestrol and double orchidectomy Gross examination of testes on section revealed in one testis a single rounded tumout 5 millimetres in diameter in the mediastimal part and in the other testis 3 similar nodalic ()4 millimetres in diameter in the mediastiman (i) 7 millimetres in diameter near the opposite side of the testis and (iii) 2 millimetres in diameter near the centre of the organ Histology (Fig. 283)—Many sections of all 4 timoust showed similar structure constitus of well differentiated tubules lined by simple cubical or low columnar epithelium with large darkly staining nuclei and slightly basophil cytoplasm. Haemorrhage had taken place into the lumina of some of the tubules. Mistoic figures were plentful and the timour elements had infiltrated amidst the surrounding testicular tubules. In structure and stanning properties the tumour tubules closely resembled those of the straight and rete tubules seen in the same sections and in spite of the distance of one of the tumours from the mediastrum it is concluded that this was their origin.

highly cellular carcinomas of other regions e.g. of the liver or stomach. Syncytial change in rapidly growing epithelial tumours does not denote specific chorionic characters, but is merely a form of growth—or perhaps of unhealth—of cells in proximity to necrosis or haemorrhage.

The rapid invasive growth of tumours of this kind and their ready extension into blood vessels explain their speedy dissemination by the blood stream to the lungs and other organs. Metastases may produce the first symptoms of disease such as haemoptysis or signs of cerebral tumour (Ahlstrom, Ross. Duncan). In a remarkable group of cases bulky chorion epithelioma like metastases develop from small structurally beingn looking testicular teratomas (Prym. Symeonids, Craver and Stewart).

No chorion epitheliomas of the testis in animals have been recorded this is not surprising since teratiomas of the testis have not been described in any animal except the horse in which they are always or nearly always of the benign

quiescent type

Can anaplastic seminomas assume chorion epithelioma like structure? All the tumours which I have seen in which much of this structure was present have consisted of embryonic epithelium like that of Figs 275 and 276 with or without more differentiated teratomatous tissues and I suspect that many of those who believe they have seen chorion epithelioma like structure related to seminoma or embryonial carcinoma have mis identified cellular areas of undifferentiated ratiomatious epithelium. However G W Nicholson informs me that he studied an unusually haemorrhagic typical well differentiated seminoma with great syncyta round the haemorrhages and Case VII above and the specimen depicted in Figs 280 and 281 exemplified the same feature

TUMOURS OF SERTOLI CELLS AND OF THE EXCRETORY DUCTS OF THE TESTIS

The excretory duets of the tests comprise the straight tubules rete efferent tubules epididymis and ductus deferens. Epithelial tumours usually malignant of all of these are very rare and of those arising within the testis particularly circful study is essential in order to distinguish them from teratomas with predominant glandilar epithelial structures. It is probable also that no sharp distinction can or should be drawn between Sertoh-cell tumours and tumours of the exerctory duets. Sertoh cells and exerctory duets are histogenetically allied non spermatic epithelia.

(1) Intra-testicular tumours of the exerctory ducts or Serioli cells

(a) Rete and allied carcinomas

I have examined two testicular tumours which I believe to be carcinomas of the straight rete or efferent tubules

Case VIII—History—A man of 31 years who had had gonorrhoea 4 years previously complianted of painful enlargement of right testis for 3 months. Watsermann reaction was found strongly positive diagnosis of syphilitic orchitut was made and course of N.A.B. injections given. Swelling perisisted and increased and 3 months later patient was admitted to hospital with punn in chest and dyspinoea and slaugerims showed multiple large rounded shadows in both long fields. Watsermann now negative. He died I month

Gordon-Taylor and Till depicted a solid spheroidal cell carcinoma of the epididymis. The common cystic dilatations of parts of the epididymis should of course, not be called adenoma "or "cystadenoma"

INTERSTITIAL CELL TUMOURS

Marked hyperplasia of Leydig's interstitial cells is of course frequent in imperfectly descended testes or in organs undergoing atrophie changes from tumours or other causes. True neoplasms of the interstitial cells, however, are rare in the human testis. Good examples and references are given by Rowlands and Nicholson (1929), Sutherland Stewart et al., Braun, Warren and Olshausen Bonser and Hawksley, and Neeve and Marsh. The tumours are usually well circumscribed, brown or orange in colour, and consist of masses of closely packed polyhedral or clongated cells with granular or vacuolated cytoplasm, which often shows faint brownish pigmentation, and in which special stains show the presence



Fig. 284—Interstitial-cell tumour with vacuolated cells from a kelpie aged 6 years. Sudan III stained frozen sections showed plentiful fat droplets in cells. (× 150)

of fine or large droplets of fat most of which is isotropic but some anisotropic (Figs 284, 285) Most of the tumours are benign, growing slowly and not producing metastases but metastases has been reported occasionally The tumours occur most frequently in adults between 30 and 50 years old When they have developed in young children there has been precocious sexual development (Sutherland . Stewart et al.)

Tumours closely similar to the human ones occur spontaneously in animals, especially in dogs (Schlotthauer et al , Innes , Huggins and Pazos) Rudduck and I found interstitial cell tumours in 16 dogs, the tumours being single in 10 and multiple or bilateral in 6 animals (Figs 284, 285) No sharp distinction can be made between nodular hyperplasia and early neoplasia of the Leydig cells The

(b) Tubular adenomas

These occur rarely in man as small multiple benign tumours in pseudo hermaphrodites or cryptorchids (Chevassu, Ide, Kruckmann) and structurally similar tumours occur occasionally in the ovary (qv). There seems little doubt that these tumours usually arise from the non-spermatic component of the seminal tubules, the Sertoli cells and that they are the counterparts of the much larger and more common Sertoli cell tumours of dogs (Schlotthauer et al Innes Huggins and Pazos). Rudduck and I studied 5 tumours of this kind from 4 dogs, bilateral growths being found in one animal. Case X above is of interest in showing points of resemblance both to carcinomas of the exerctory ducts and multiple adenomas of the testis it suggests that no sharp line of separation need be drawn between exerctory duct epithelium and its tumours on the one hand and Sertoli cells and their tumours on the other. In my opinion this view is supported also by study of the canine tumours the structure of some of which is compatible with an origin from either Sertoli cells or rete ducts.

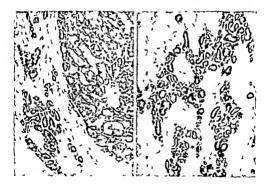


Fig 283 - Case & Multiple tubular adenomas (x 80)

(2) Fytra testicular tumours of the excretory ducts

Epithelial tumours of the epidadymis and ductus describes are very rare Rowlands and Nicholson (1909) described a squamous cell carenoma of the epidadymis and Thompson (1936) reported and collected examples of adeno carenoma of this organ. While the figure of Thompson's Case 33 depicts un doubted adenocarenoma this diagnosis is dubious in his Fig 9 which shows a growth exactly like that which I have regarded as a benign lymphangiom (Fig. 347).

by the disappearance of hormonal disturbances following removal of the tumour in some cases, and their reappearance with the growth of recurrent tumour or metastases. Interstitual cell tumours constitute a special case in which precocious puberty may be attributed to the direct effects of androgen from the secreting tumour cells (ii) The tumours, by producing testicular atrophy or other secondary effects on the gonaidl tissues, may disturb the balance of sex hormones (iii) Some victims of testicular tumour may already have had some previous endocrine imbalance, as in pseudo hermaphrodites or cryptorchids. Of these three possibilities the first seems the most probable. But before speculating further, we need further careful hormonal assays from eases of testicular tumours and correlation of the findings with careful histological studies of the responsible tumours. To this end we particularly need clear ideas regarding the histogenesis of the tumours unclouded by misconceptions about the origin of seminomas and about the use of the capacious piecon hole labelled, "embryonal carenoma".

SUMMARY OF THE NATURE AND CLASSIFICATION OF TESTICULAR TUMOURS

The evidence presented in this chapter warrants the following grouping and nomenclature of the evithelial and allied tumours of the testis

(1) Seminomas

These are, as Chevassu held, seminal carcinomas. They arise from the spermatic cells of the tubules, and are appropriately called also *spermatocitomas*. They are unrelated histogenetically to teratomas, but not infrequently arise in testes already continuing teratomas.

(2) Teratomas

Malignant or benign, these are the counterparts of the ovarian and other teratomas. They frequently contain much cellular undifferentiated epithelal tissue, which on the one hand by superficially mimicking seminoma may promote confusion of the two classes of tumour under the designation "embryonal card noma" and on the other hand may undergo haemorrhagic changes and assume a chorion epithelioma like structure. Most "chorion-epithelioma" of the testis are only rapidly growing haemorrhagic territomas, a few of them may be haemorrhagic seminomas.

(3) Carcinomas or adenomas of the excretory ducts

These may be either (a) intra testicular, arising from the epithelium of the straight tubules, rete or efferent tubules, or (b) extra testicular, arising in the epididymis. Alhed to, and perhaps not to be sharply separated from timours of the intra testicular excretory ducts, are Serioli cell timours or tubular adenomas.

(4) Interstitual-cell tumours

These closely resemble their parent tissue, the cells of Leydig

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experimental production of interstitual cell tumours in mice by oestrogens is described in Chapter 4

HORMONAL RESULTS OF TESTICULAR TUMOURS

Tumours of the testis and their metastases are often associated with hormonal disturbances, which though of great interest, are still far from fully understood. These results include increased urinary exerction of gonadotrophins, sometimes sufficient to give a positive Aschheim Zondek test of intensity as great as that in normal pregnancy or in true chorion epithelioma, and hyperplasia and secretory activity of the male breast. Instances of these results have been reported by Handfield Jones Prym, Sas. Heidrich et al., Mackenzie and Ratner Storjohann Symeonidis. Duncan and Ferguson et al. The fact that in many such cases the tumours have consisted wholly or partly of chorion epithelioma like growth has been advanced in support of Schlagenhaufer's view that the testicular growths of this kind are indeed chorionic in nature and essentially the same as the true gestational chorion epitheliomas and this view appeared to be supported by the very high titre of the Aschheim Zondek test in some of the cases.

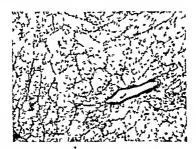


Fig. 285—Interstitual-cell tumour with compressed clear-celled structure from a dog. Sudan HI stained frozen sections showed much fat in the cells. (\times 100)

That the problem is a more complex one however, is shown by the following facts: (a) Seminomas and testerular teratomas divord of chorion-epithelioma like itsue can produce similar though usually not so intense endocrine disturbances (Zondek Ferguson et al.) (b) Gynaccomastia occurs in many conditions other than testicular tumours including testicular atrophy adrenal cortical tumours pituitary tumours or hepatic disease (Herzenberg Busch Ahlström, Bergonzi, Weber)

We may speculate on the several possible ways in which testicular tumours may be associated with endocrine disturbances (i) The tumour itself may produce hormones or substances capable of disturbing hormonal balance this is supported

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(3) Age meidence

Prostatic carcinoma is notable as occurring later in life than any other form of malignant disease, appearing on an average a decade later than carcinomas in the aggregate. About three quarters of clinical cases are in the seventh and eighth decades, the peak of the age distribution curve is towards the end of the seventh decade, and most of the deaths from this disease take place in the eighth decade (Bumpus Gordon) The mean age of my 40 necropsy cases was The disease is very rare before the age of 40

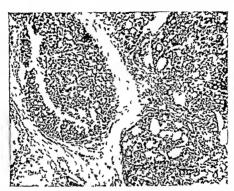


Fig 286 -- Prostatic adenocarcinoma from an Alsatian dog 9 years old (Case 1 of Ruddick and Willis) (x 80)

(4) Causation

The view that benign in perplasia is a significant pre cancerous lesion and that carcinoma often supervenes on it is difficult either to prove or disprove This view is based mainly on the closely similar age incidence of the two diseases, the probability-still however, unproved-that both are related to endocrine disturbances (Moore), and the frequent coexistence of hyperplasia with caremona The last argument, however, carries little weight, for most prostates from middle aged or old men show some degree of nodular hyperplasta Hence, while it is quite possible, even probable, that hyperplasia and neoplasia of the prostate are related, it remains for future research to prove and define the relationship

There is no substantial evidence to support the view that inflammatory diseases predispose to carcinoma of the prostate The occasional coexistence of veneral infections, tuberculous or calculi is no more than coincidental

(5) Prostatic carcinoma in animals

Adenocarcinoma is not unusual in elderly dogs (Feldman, Rudduck and Willis, Schlotthauer and Millar, and see Fig 286) but has only rarely been

CHAPTER 34

CARCINOMA OF THE PROSTATE

FREQUENCY AGE INCIDENCE CAUSATION

(1) Frequency

BECAUSE prostatic cancer often escapes clinical diagnosis its real frequency cannot be estimated from registered mortality figures. The disease probably accounts at present for about one tenth of male deaths from cancer e.g. in the United States of America in 1938. 115 per cent of registered deaths from cancer were attributed to prostatic cancer (Go don). Most necropsy series record between 5 and 15 per cent of fatal carcinomas in males as prostatic, e.g. 40 of 635 cases (6 per cent) in my series in Table V. Chapter 5.

Several workers by thorough examination of prostates surgically removed or obtained post mortem have claimed to show that small symptomicss growths structurally carcinomatous are present in a surprisingly high proportion of men past middle age e.g. 13 per cent of men over 60 years of ag. (Mur) 18 per cent of men of average age 69 years (Gaynor) 14 per cent of men over 40 (Rich) 18 per cent of men over 40 (Moore) 17 per cent of men over 50 (Kahler) and 46 per cent of men over 50 (Baron and Angrist). The magnitudes of and especially the great discrepancies between these estimates raise doubts regarding the histological criteria for the diagnosis of carcinoma adopted by some of these workers Baron and Angust's conclusion that nearly one half of the male population over 50 years of age is affected by prostatic cancer seems incredible While all experienced pathologists will agree that routine microscopical examin ation will disclose undoubted early carcinoma in a proportion of men in whom it has not been suspected elinically or on naked eye examination of the prostate the exact proportion is still I think very uncertain. The histological distinction between being hyperplasia and earcinoma is not always easy to make and there my well be room for much difference of opinion regarding the diagnosis of carcinoma in many routinely examined prostates. However it would not be a matter for great surprise if it were proved that say 5 or 10 per cent of men in the seventh and eighth decades had unsuspected prostatic cancers. The securing discrepancy between such a finding and the clinical frequency of the disease would readily be accounted for by the well known fact that prostatic cancer often

in the elderly (2) Race

Comparisons of the incidence of prostatic cancer in different races are quite unreliable. The factor of differences of age composition—still largely unknown for many non European peoples—is of particular significance in this disease which is chiefly one of old age. The fact that prostatic cancer has only occasionally been recorded in the Chinese (Moore) is of lattle significance. Cooray however records that 50 of 1815 careinoma biopsies in Ceylon were from the prostate and American records include many cases in Negroes.

grows slowly and symptomiessly and by the high mortality from other causes

hyperplastic or inflamed prostatic tissue, and care must be taken not to mistake these for carcinoma

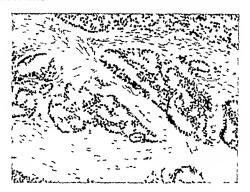


Fig. 288 —Well differentiated prostatic adenocarcinoma (> 150)

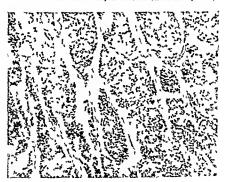


Fig. 289 -Imperfectly differentiated prostatic adenocarcinoma (× 120)

The stromal reactions evoked by prostatic carcinoma. These deserve special note. Familiar to all clinicians and pathologists is the osteoplasia induced by metastatic growths in bones, leading to ivory condensation of parts of the affected

recorded in other mammals
Engle and Stout saw multifocal prostatic care noma without metastases in an old monkey. By means of benzpyrene Moore and Melehonna produced squamous cell careinomas but no adenocarcinomas in the rat's prostate
Recently however Horning obtained transplantable adeno careinomas in inbred mice, from subcutaneous prostatic grafts wrapped round methylcholanthrene crystals

STRUCTURE

The following structural variants are seen in prostatic carcinomas—several or all of them may be seen in one tumour

(a) Adenocarcinoma consisting of distinct tubules or acini is by far the commonest type of growth. Almost all tumours show glandular structure in parts, though the degree of differentiation varies. Many tumours consist largely



Fig. 287 —A metastasis of well differentiated prostatic adenocarcinoma in a certical lymph gland, the primary growth had been symptomiess and unsuspected. (× 120)

of well differentiated small acms so characteristic that their prostatic origin is readily detected or suspected by the experienced microscopist (Figs. 287–289). Other tumours show tubular cystic or papillary structure not diagnostic of a prostatic origin. Mucoid carcinoma as in the case described by Klissurow is rare

- (b) Spheroidal celled carcinoma simplex appears in the scirrhous or desimo plastic form less commonly in the cellular anaplastic form. As Cappell has shown diffuse carcinoma may simulate and his no doubt often been misdiag nosed as sarcoma or a tumour consisting partly of well differentiated and partly of diffuse carcinoma may be called carcino sarcoma:
- (c) Squamous metoplassa in parts of an adenocarenoma is rate. Nicholson (1923) referred to several cases. Kahler saw squamous celled carenoma in 6 of 195 cases. Areas of squamous metaplassa are sometimes present in simple.

cures Many untreated cases of this disease progress slowly and with symptomatic remissions, and in some treated cases, even those initially responding favourably the growths have nevertheless progressed and metastases have developed later Hormonal therapy cannot yet be regarded as effecting more than temporary suppression of some tumours

SPREAD AND METASTASIS

(1) Local spread

The extension of carcinoma to the capsule of the organ and to the periprostatic tissues takes place by the usual routes, namely tissue spaces, lymphatics and small veins. Warren et al and Kahler have stressed the frequency of permeation of perineural lymphatics but in my opinion have given it undue prominence. The hypothesis that this is a usual route by which secondary deposits reach the lumba: vertebrae and pelvice bones is not in accord with the distribution of skeletal metastases disclosed by thorough necropsies (see below). Gross invasion of the bladder, rectal wall and other pelvice soft tissues occurs in advanced cases. Invasion of the erectile tissues of the penis may cause priapism (Fronz and Alyea, Guibal and Pavic)

(2) Metastases in lymph glands

Lymph glands are affected, sometimes very extensively, in a high proportion of fatal cases, e.g. in 77 per cent of Muir s cases, the groups of glands involved being the internal iliac external iliac, lumbar inguinal, thoracic and supraclawcular, in that order of frequency. Lymph nodal deposits were present in 26 of my 40 necropsies 1c 65 per cent. Lundsgaard reported a case in which large cervical growths were the first signs of a small symptomiess primary growth. A specimen which I examined consisted of a mass of growth 6 contimetres in diameter in the axillary lymph glands, excised as probable Hodgkin's disease, microscopically, this showed the typical structure of small acinar prostatic adeno carcinoma, and rectal examination then revealed hard nodular enlargement of the prostate

(3) Blood-borne metastases

(a) In viscera

Blood borne metastases are present in the viscera in about 40 per cent of fatal cases, the organs most frequently affected being the lungs, liver and adrenals

(b) In bones

Skeletal metastases develop in a high proportion of cases—from 30 to 70 per cent in various reported series. The higher estimates are probably nearest the truth, the frequency with which these metastases are recorded depending of course upon the thoroughness of the radiographic or necropsy examination of the skeleton. Skeletal metastases not infrequently produce the first or main symptoms of disease (Willis, 1934), persistent lumbago', sciatica' or other 'rheu' matic' pains, or obscure bone tumours or pathological fractures in elderly men should always excite suspicion of possible cancer of the prostate. So also should

bones and to irregular ostoophytes (see below). The fact that prostatic cancer in bone evokes osteoplasia almost regularly and with much greater frequency than any other kind of tumour strongly suggests that this reaction is due to some specific diffusible substance liberated from the tumour cells. Occasionally, metaplastic formation of bone occurs in the connective tissue stroma of primary prostatic cancer or in metastases in soft tissue as in Nicholson's case (1924 Fig. 77) and Schmorl's case referred to in Chapter 8. This special bone evoking property of prostatic carcinoma may well be related to its phosphatase activity, it is possible that the secretion of acid phosphatase by prostatic epithelium and of alkaline phosphatase by osteoblasts may together be concerned in the osteo plastic reaction.

METABOLIC PECULIARITIES OF PROSTATIC CARCINOMA

(1) Secretion of phosphatase

Prostatic carcinoma shares with normal prostatic epithelium the power of secreting large amounts of acid phosphatase (Gutman et al. Watkinson et al. Haddow). Kutseher and co workers first discovered that normal adult prostatic tissue is very rich in a phosphatase with optimal activity at pH 5.0. The Gutmans then showed that this enzyme was plantiful also in cancerous prostatic epithelium in both primary and secondary growths and later that patients with metastases in bones usually showed markedly increased amounts of acid phosphatase in the blood serum. In cases of non prostatic carcinoma with skeletal metastases and in most cases of Paget's disease, raised values of serum acid phosphatase were seldom found so that this test may sometimes be of value in the differential diagnosis of sclerosing lesions of bone of doubtful nature. The amount of alkaline phosphatase, in the serum in various bone diseases fluctuates independently of that of the acid phosphatase, it depends not on secretory activity of epithelial cells, but on osteoblastic activity either in reactive states of bone or in osteosenic tumours (of v).

(2) Hormonal control

It has long been recognized that castration causes atrophic changes in the prostate-indeed John Hunter was aware of this-and beneficial results have been obtained by castration in cases of benign, and more recently of cancerous enlargement of the prostate. The discovery that administration of pestrogens also benefited some patients with carcinoma of the prostate has led to formulation of the general principle that the growth of prostatic cancer is encouraged by androgens and inhibited by oestrogens Progressive histological studies and also estimations of the level of serum acid phosphatase following custration or oestrogen treatment support this view (Watkinson et al., Huggins and Hodges Schenken et al Fergusson and Pagel) It is now apparent that the characteristic enithelia of the normal prostate and of the benign and (some) malignant tumours of the gland have much in common as regards their phosphatase content their dependence upon androgenic activity and their reaction to orchidectomy or the administration of oestrogens (Haddow) Although striking alleviation has been obtained in many cases of prostatic cancer by castration or hormonal treatment it is still too soon to conclude that these measures may effect permanent

common sites of metastases from other tumours, and doubtless for the same reason namely that they are large bones containing red marrow. Radiologists, having their attention focused on these bones because of the prevalent teaching regarding their mode of involvement from prostate cancer, and also finding them a convenient field in which to scarch for metastatic lesions, naturally discover such lesions here more often than they discover them elsewhere, and so obtain a false impression of their relative frequency



Fig 291 -Osteoplastic vertebral metastasis of the tumour shown in Fig 288 (x 150)

The route of dissemination of metastases in the skeleton is of course bound up with their distribution. My necropsv experience typified in Fig. 292, leads me to conclude that this takes place mainly by the usual routes, namely by invasion of veins or major lymphatics from the prostatic growth or its lymph nodal metas tases, embolic dissemination to the lungs, and thence to the bones via the systemic Batson has advanced the interesting hypothesis that the rich vertebral venous plexus is the usual route of dissemination of prostatic and other growths to the axial skeleton While recognizing that this route may well be an important auxiliary one after establishment of growths in the vertebral region and of collateral channels of flow, following tumour invasion of large pelvic or vertebral veins, there is no reason to suppose that it superscdes the well established route via the lungs Batson, like many other workers, regards the not infrequent freedom of the lungs from growths in eases with metastases clsewhere as a ' paradox" But, of course, adequate microscopie study of such lungs will often confirm Schmidt's finding of arrested tumour emboli in pulmonary arterioles, and will show that the "paradox ' is largely imaginary (see Chapter 10) several cases of disseminated prostatic caneer without grossly obvious metastases in the lungs. I have searched for and found minute metastases or arrested tumour emboli in the lungs It is quite probable however, that a prostatic growth or its

radiographic discovery of multiple osteoplastic lesions in bones with rare exceptions osteoplastic metastatic earenoma in men is prostatic in origin (Figs / 290 291). Radiographic-illy extensive osteoplastic carcinosis can be mistaken for Paget's disease. The metastases of prostatic carcinoma in bone have been well described by you Recklinghausen. Kaufmann. Fischer Defoy. Axhausen Joll Purckhauer and Zemgulys.

The distribution of the metastases in the skeleton deserves special comment It is often asserted mainly on radiographic evidence that the pelvis lumbar-vertebrae and upper ends of the femora are affected with disproportionate frequency whence it is concluded that these bones are usually reached by direct extension of the growth from the prostate in lymphatics or other channels

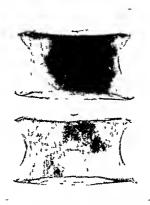


Fig. 290—Skiagram of two lumbar vertebrae containing osteoplastic metastases of prostatic carcinoma.

This assumption is more than doubtful. Careful necropsy work shows that early metastases of prostate careinoma in bones are often well circumscribed rounded masses with a scattered distribution very similar to that of metastases from other or primary tumours. Fig. 292 depicts the distribution of metastases in the vertebrae in 4 cases of prostate careinoma in which thorough necropsy section of these bones was undertaken. These show scattered distributions of the growths with no evidence of a centrifugal relationship to the primary growth—distributions which might equally well have been found with carcinomas of the breast or stomach or thyroid. It is of course true that the lumbar vertebrae and pelvice bones are common sites of metastases from prostatic cancer just as they are

the pelvis and lumbar vertebrae. This opinion was based on the frequent finding of cancerous permeation of these lymphatics in the periprostatic tissues in 7 cases with metastases in these bones. It must be noted, however, that 4 of the 7 cases had visible metastases in the lungs, that there is no record of microscopical search of the lungs for tumour emboli in the other 3 cases, that only the pelvis and lumbar vertebrae were subjected to special examination and there was no necropsy study of the distribution of tumours in other parts of the skeleton, and that the authors admit that while perineural permeation was common in the periprostatic tissues "very little evidence was found of involvement of nerves or of their lymphatics extending towards the bony pelvis."

CARCINOMA OF THE SEMINAL VESICLES

Authentic examples of this disease are very rare. Clinically, they are either regarded as carcinomas of the prostate or they cause errors of diagnosis by their metastases. Trachsler reviewed provious records, and reported a case in which vertebral metastases led to a diagnosis of primary spinal disease. Junghanns reported a case of 's sarcoma"—possibly anaplastic carcinoma—of the seminal vesicles with cerebral metastases which simulated primary brain tumour

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lymph nodal metastases may sometimes invade neighbouring vertebral veins whence the tumour may spread into the adjacent bones, or that following establishment of secondary growths in the vertebrae by this or the more usual embolic route, invaded vertebral veins may be a route of local direct or embolic spread within the bones or from one bone to another. The involvement of several neighbouring vertebrae in a large mass of secondary growth as in Case I Fig. 292

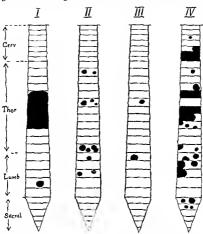


Fig. 292.—Diagram to show distribution of spinal metastases in 4 cases of prostatic carcinoma. Case I aged 83. all other bones clear including pelvies small metastases present in lungs. Case II aged 66. metastases also in stermini and skull but not in pelvis. no visible metastases.

Case III aged 70 metastases also in petvis and sternum small metastases present in lungs
Case IV aged 64 metastases also in petvis and sternum small metastases present in lungs

may well be due to such local spread from a single initial metastasis in one of the bones. It may be mentioned too that Roberts studying the spiril metastases of prostatic cancer found extensive plaques of growth on the deep surfaces of the laminae and ligaments and suggested that the lymphatics of the plagaments and neighbouring itssue might be an important route of extension of the growths within the spine from bone to bone.

Warren and co workers while agreeing that the metastasis of prostatic cancer to bones often takes place by the blood stream advanced reasons for believing that perineural lymphatics afford an important auxiliary route of metastasis to

CHAPTER 35

EPIDERMOID CARCINOMA OF THE PENIS AND SCROTUM

In structure and behaviour tumours of the epidermis of the serotum and penis resemble those of the skin generally (q v) Basil cell growths and tumours of the cutaneous glands are, however, very true in these sites Because of differences in causation epidermoid growths of the penis and serotum must be considered separately from those of the rest of the skin and from each other. As in other situations no sharp distinction can be made between papilloma and carcinoma, the one is only the non invasive form, and the other the invasive form of the same kind of growth, and all transitions are seen

EPIDERMOID CARCINOMA OF THE PENIS

(I) Incidence and causation

(a) Frequency and race

Almost all penile neoplasms are epidermoid careinomas, careinomas of the penile urethra are rare, and non epithelial tumours of the penis are rarer still some of the few supposed instances (e.g. the 'endothelioma' reported by Colmers) clearly being careinomatous. In most European countries and in America penile cancer is a relatively infrequent tumour, e.g. in England and Wales during 1930–1932 there were 496 deaths from penile cancer as compared for example with 18,876 deaths from gastric cancer. 3,225 from lingual cancer and 2,668 from vesical cancer in males (Registrar General's Decennial Supplement, 1938).

Although accurate comparisons are not possible it is clear that penile cancer is much commoner amongst the Oriental races, especially the Indians and Chinese than amongst Europeans. Thus in Nath and Grewal's analysis penile cancer ranked high in the lists of tumours studied in Indian hospitals, accounting for about one tenth of all cases of mahgnant disease in males in most communities, and it accounted for 248 of 1,815 carcinoma biopsics reported by Cooray from Ceylon and for 18 per cent of cancers in Chinese (Ngai)

(b) Circumcision

Circumcision is undoubtedly the main factor responsible for the racial differences of incidence of penile cancer, and no genetic differences in susceptibility need be postulated Amongst the Jews of all countries, who regularly circumcise in infancy, penile cancer is very rare, perhaps indeed non existent (Sorsby) Amongst Mohammedans, who defer circumcision until childhood or adolescence, the disease occurs occasionally The sharp contrast between the ratity of penile cancer in Mohammedans and its great frequency in the uncircum cised Hindus in the same communities is well shown in Nath and Grewal's figures Ngai found phimosis in 87 of 88 Chinese patients Climcians and pathologists have of course long recognized that penile cancer in Europeans is

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glans or prepuce and without signs of infiltration of the deeper tissue. They may long remain in this stage, slowly extending, but eventually invasive carcinoma supervenes

(3) Spread and metastasis

Besides extending to and perforating the overlying prepuce, the tumours often invade the urethra and corpara cavernosa and spangiosa. Some tumours spread preferentially within the vascular spaces of the erectile tissue (Kuttner, Colmers) and it is possible that local embolic metastases may also occur in this tissue for areas of growth apparently separate from the main mass are sometime to be found in more proximal parts of the erectile bodies

Metastases in lymph glands develop at some stage of the disease in a high proportion of cases, 60 per cent according to Barney Although enlargement of the inguinal glands is usually present at an early stage, this is often due to inflammation only, tumour metastasis usually occurring relatively late (Kuttner, Lane Claypon) Microscopical examination of the glands is therefore important for prognosis. Kuttner found that in occasional eases the pelvic lymph glands were affected earlier than the inguinal glands

Blood borne metastases have only occasionally been reported (Barney, Kuttner, Ngas)

EPIDERMOID CARCINOMA OF THE SCROTUM

(1) Incidence and causation

(a) Frequency and race

In England and Wales deaths from scrotalcancer are about half as numerous as those from penile cancer, e.g. 209 and 496 cases respectively during the years In native races and non industrialized countries, cancer of the scrotum occurs but rarely, if ever, the Kennaways could find no instances of this disease even from countries where penile cancer is common

(b) Occupational and social factors

Chimney sweeps' cancer was the first tumour to be clearly recognized as occupational, by Pott in 1775 The most recent and detailed accounts of occupa tional cancer of the scrotum are those of Hueper (1942) and of Henry (1946) while the Kennaways' papers also give valuable analyses. In the majority of cases scrotal cancer is clearly attributable to occupational factors occurring in chimney sweeps, cotton mule spinners and gas, tar pitch and creosote workers and there is little doubt that benzpyrene and other carcinogenic hydrocarbons are the offending agents Further, victims of this disease in occupations not recognized as hazardous almost all belong to the industrial or other manual labouring classes professional and clerical workers being almost exempt from scrotal cancer This therefore appears to be a form of cancer that is wholly, or almost wholly dependent on environmental factors" (Kennaway and Kennaway) The Kennaways suggest that those persons who from chance

much more frequent in the unercumered than in the circumcised and that phimosis is present in a high proportion of patients with this disease more than one half of them according to Lane Claypon. It is probable that pende cancer could be eliminated by general adoption of circumcision in infancy. It is for future research to show whether or not carcinogenic substances are generated in retained sinegina.

(c) Other possible carcinogenic factors

As the Kennaways have shown careinoma of the penis contrasts sharply with careinoma of the scrotum in that its incidence shows no distinct relationship to occupation or social class. This supports the view that the main factor in causation is the presence of the prepuce, and that extrinsic careinogens play little or no part. Although examples are recorded of careinomas arising in or near the sears of former chances (Barney, Leighton) it is doubtful whether venereal or other infections predispose significantly to the disease.

(d) The distribution of the tumours

This also supports the view that extrinsic factors are of little importance in causation. The almost invariable sites of origin are the plans or inner surface of the prepuee earcinoma of the skin of the penis or of the outer surface of the prepuee is rare.

(e) Age

The mean age of European patients at the time of treatment is between 52 and 54 (Lane Claypon) and the disease has only occasionally been observed in men under 30 (references by Leighton). In Orientals, however, the average age of patients is about a decade less than in Europeans e.g. 44 in Ngai s series.

(f) Penile carcinoma in animals

This is one of the commonest tumours in the horse and it occurs also in the ox dog and cat (Feldman). Rudduck and I saw also two examples of carcinoma of the shoominal will close to the prepuce in dogs.

(2) Structure and growth

The tumours are papillary or infiltrating epidermoid growths similar to those of the rest of the skin. In their early stages they may long remain superficial and papillomatous and this papillomatous change may take place over a wide area of the surface of the glans and prepuce or multiple areas of growth may be found Papillary tumours may form large exuberant masses before showing much invasiveness but this does not justify their separation as a distinct group from the more invasive uherative form of growth. It is not unusual for a well advanced growth to remain long hidden and unsuspected in a patient with phimosis

A rare form of tumour is intra-epidermal carcinoma in situ this is the counterpart of Bowen's disease of the skin and has been called 'Paget's disease of the penis and erythroplasia, names which as urged in Chapter 14 denote only variants of the one kind of lesion. Intra epidermal carcinoma of the penis appears as single or multiple shiny red or encrusted patches, flush with the surface of the

glans or prepuce and without signs of infiltration of the deeper tissue. They may long remain in this stage, slowly extending but eventually invasive carcinoma supervenes

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or professional necessity wash most are the least liable to scrotal cancer that in cases of this disease in which no definite occupational hazard has existed the disease may be due to lack of cleanliness in those exposed to coal smoke. in other words, possibly all town dwellers are in some slight degree liable to chimney sweeps cancer

(c) Site

Most of the tumours are situated on the anterior and lateral aspects of the scrotum, and rather more often on the left side than on the right (Henry)

(d) Age

When in Pott s day boys were engaged as chimney sweeps it was not unusual for scrotal cancer to occur in children or adolescents (references by Hueper) With increasing recognition of this and allied occupational risks and the intro duction of protective legislation however vouthful cases ceased to occur and the mean age of the victims of scrotal cancer steadily increased until it now lies late in the sixth or in the seventh decade (Henry). Henry also draws attention to the long periods of exposure necessary for the induction of the disease-from 16 to 50 years after commencing work in the hazardous occupation. The disease may develop many years-up to 35 years-after retirement from work. Henry mentions one man who started work in the mule room at the age of 6 and developed serotal carcinoma at 75 10 years after retirement

(2) Structure, growth and metastasis

What has already been said of epidermoid earcinoma of the penis and of the skin generally applies to that of the scrotum Benign warts may long precede invasive malignancy Multiple growths are fairly common. The tumours are of the usual cornifying type seldom growing very rapidly but eventually extending widely to surrounding parts and ulcerating, producing inflammatory enlargement of the incumal lymph glands at early stages and metastases in the glands at later stages and occasionally disseminating by the blood stream

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is certainly false. (The rather distinctive 'Hurthle cell' adenoma is considered along with careinoma)

(2) Behaviour

Most thyroid adenomas grow only slowly, and cessation of growth with degenerative changes is frequent. Yet a long standing apparently stationary tumour may become a "malignant adenoma' and produce metastases In addition to histological anaplasia and mitotic activity of suspicious degree in a tumour regarded as an adenoma', there are two other structural features which for prognostic purposes place tumours of otherwise 'benign' appearance in the malignant adenoma' class. These are (a) predominant papillary structure, and (b) invasion of blood vessels



Fig 293 - Colloid adenoma with much oedematous stroma (× 90)

(a) Papillary adenomas cannot be distinguished from papillary carcinomas, Dunhill in his large experience saw only two tumours which he regarded as "benign papillomas', and one of these later recurred I have seen two instances of infiltrative recurrence of tumours initially diagnosed as papillary adenomas Here is the history of one of these

Case I-In April 1932 a woman of 44 years had had a slowly enlarging rounded tumour in her neck for 7 years. At operation a well-circumscribed cystic. adenoma 10 centimetres in diameter was evacuated and enucleated Microscopical diagnosis was highly papillary adenoma potentially malignant. Slow recurrence took place and in June 1935 a firm ill-defined mass of growth was excised. This again showed well organized papillary growth identical with that removed 3 years earlier Further recurrence later took place and was deemed moperable because of adhesion to the trachea

CHAPTER 36

EPITHELIAL TUMOURS OF THE THYROID GLAND

In the thyroid gland as in many other organs, no sharp separation of epithelial hyperplasias being tumours and malignant tumours is possible Modular areas of hyperplasia in gottrous organs become adenomatous structural distinction between adenoma and caremoma is often impossible, and not a few beingn adenomas of long duration eventually prove malignant by invading blood vessels and metastasizing sometimes with little or no change of structure of course it is convenient and necessary to assign thyroid overgrowths to one or another group and in most cases the behaviour of the lesions corresponds with

blood vessels and metastasizing sometimes with little or no change of structure Of course it is convenient and necessary to assign thyroid overgrowths to one or another group and in most cases the behaviour of the lesions corresponds with the experienced pathologist's opinion. An adenoma is a well circumscribed encapsulated tumour with no evidence of invasive growth or metastasis. A corcumon as a tumour of any structure which shows evidence of invasive growth or metastasis. Its histological structure usually betrays its malignancy but is sometimes being in appearance resembling in part that of any of the forms of adenoma or even of normal thyroid ussue. The rare invited tumours containing both epithelial and mesenchymal components will require separate consideration

ADENOMAS

I do not propose to repeat in detail the well known features of these common tumours (see Marine, Tebbutt and Woodhill and Joll) Most of them arise in gotrous thyroids they are therefore more frequent in endemic gotrous regions than in others, they affect women more than men and may be single or multiple. They vary greatly in naked eye appearance, the tissue of some having the typical vesicular structure of normal thyroid or colloid gotire and that of others being solid and opaque, cystic change, haemorrhage pigmentation fibrosis and calcification are frequent.

(1) Microscopic structure

This, like the naked eye appearance varies greatly. Colloid filled vesicles of all sizes and shapes well differentiated acini devoid of colloid poorly differentiated acini or almost diffuse sheets of epithelial cells, and papillary structures with or without colloid, are found (Figs. 293-294). The stroma is often oedematous poorly fibrous and plentiful sometimes so abundant as to give the tumours a semi fluid translucent appearance. Some tumours show predominance of one or other type of structure others show several or all of the possible structural variants. Mitosis is seartly in benign adenomas, whether of well differentiated vesicular or poorly differentiated types. Squamous metaplasia as in the specimen depicted by Nicholson in his Fig. 71 is rare. Attempts to subdivide adenomas into colloid, foetal and mixed varieties are futile and unnecessary and persistence of the term. foetal is unfortunate, for Wolfer's view that adenomas of predominantly non colloid structure arose from rests. of immature issue

(b) Age incidence

This differs little from that of carcinoma in general. The peak of the age distribution curve of Pack and Le Fevre's clinical series lay in the second half of the sixth decade, and the mean age was 53 years. The mean age of males in Pember ton's series was 53, of females 48, and 70 per cent of all cases were between the ages of 40 and 70 years. The mean age at death of my 9 necropsy cases was 70 years. The disease rarely appears in people less than 35 years old, but it may occur even in childhood, e.g. Pemberton's series included 4 patients under 10, all girls, the youngest aged 7

(c) Sex

In most series of cases there is a decided excess of females over males, e.g. 3 to 1 in the mortality figures of England and Wales 1918-30 (Joll), 3 to 1 in Pack and Le Fevre's clinical series, and 17 to 1 in Pemberton's series. Cooray's Cingalese patients were 24 women and 14 men, and all 7 of Quinland and Cuff's Negro patients were women.

(d) Previous goitre

This is recorded in a high proportion of cases—between 25 and 60 per cent of cases in populations in which gotte is not specially prevalent, and in even higher proportions of cases in goilrous regions. It is clear that nodular gotte and adenoma predispose to carcinoma (see Wegelin's figures cited above). In a high proportion of cases, probably the majority, carcinomas arise in pre evisting adenomis. Graham and others placed this proportion as high as 90 per cent but, as Pembe ton has pointed out some long standing supposedly being adenomas. In may possess low grade malignancy ab unito. Cole et al., in a good discussion of nodular gotte as a pre cancerous lesion, found that 37 per cent of their carcinomas definitely arose in adenomas but considered that the actual proportion was certainly greater than this the carcinoma doubtless having submerged the original adenoma in many cases.

(2) Adenonias and carcinomas of the thyroid in animals

Thyroid adenomas and carcinomas—it is often uncertain which—have been reported in many species of animals, including fish as well as dogs, horses cattle, sheep guinea pigs and rats (Ewald, Wegelin, Feldman, Hellwig, Davis). As in man so in animals, goitre usually precedes the development of tumous. Metas tasizing carcinomas of the thyroid are common in dogs, especially in endemic goitrous areas, large veins are often invaded by tumours and metastrises occur principally in the lungs (Davis).

(3) Structure

Individual tumours may show predominance of one or another of the following types of structure or several or all of these variants may be found in one tumour

(a) Colloid containing vesicular adenocarcinoma, resembling normal thyroid

The discovery that an enucleated tumour has a papillary structure however highly organized and quiescent in appearance, calls for at least partial thyroidec tomy of the tumour bearing part of the organ and a guarded prognosis

(b) Demonstrable invasion of small vens in an adenoma or its capsule places it unequivocally in the malignant class. As Ehrhardt Erdheim Graham Warren and Dunhill have all shown later recurrence or metastasis from such tumours is frequent however benign "their structure."

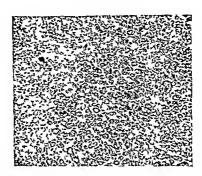


Fig. 294—So-called foetal adenoma with small vesicles without colloid and undifferentiated diffusely scattered epithelium. (× 75)

CARCINOMAS

(1) Frequency and causation

(a) Frequency

The frequency of cancer differs greatly in different communities, according to the provalence of goitre. Thus Betard and Dunet (cited by Wegelin) concluded that in endemic gostrows regions from 2.5 to 4 per cent of all malignant tumours arose in the thyroid but in goitre free areas less than 0.5 per cent. Wegelin noted the much greater incidence of thyroid cancer in necropsies in Berne the centre of a gostrous area than in Vienna Prague Betlin or the United States of America. The ratio of malignant to non malignant enlargements of the thyroid seen in hospital practice in Great Britain is indicated by Vaux effigures. In 6 found 25 cases of malignant disea e in 722 cases of gostre (3.5 per cent) and cited other series showing proportions ranging from 1 to 5 per cent Various native races get thyroid cancer e.g. the Cingalese (Cooray), Tangan yikans (Connell) Bantus (Strachan). Negroes (Obunland and Cuff)

vesicular characters is a frequent form of growth, inseparable from papillary adenoma (Figs 296 and 300). This is the kind of growth which is prone to metastasize locally to the cervical lymph glands and to grow slowly there, simulating a 'lateral aberrant thyroid' (see below)

- (d) Carcinoma simplex occurs alone or along with other structural variants. It may be of alveolar polyhedral celled type, or may be diffuse and pleo morphic celled and readily mistaken for sarcoma (Fig 297). Multinu cleated giant tumour cells are common in anaplastic carcinoma. There is no doubt that most of the reported 'sarcomas' and "carcino sarcomas' of the thyroid have been anaplastic carcinomas.
- (e) Squamous cell structure resulting from metaplasia is rare (Nicholson, Pemberton)
- (f) So called " Hurthle cell " structure (see below)



Fig. 297—Diffuse pleomorphic-celled part of the primary growth from the same case as Fig. 296 (×120)

Thyroid carcinoma is remarkable for the diversity of structure which may be found in one timour, as in the timour described by Rosenthal and Willis in the timour depicted in Figs 296 and 297, and in Case IV below On the other hand, some of the cystic papillary growths show remarkable uniformity of structure during a long metastatic career, and some of the highly anaplastic growths consist of similar diffusely cellular tissue throughout (For good accounts and illustrations of the range of structure in thyroid carcinomas see Bell, Graham, Smith et al., Dunhill, Haagensen, Vaux and Joll)

(4) "Hurthle-cell' tumours

The so called Hurthle cell" tumours require separate mention, because of their rather distinctive structure and because of the doubtful propriety of the name

or colloid goitre (Fig 295) is the structure which, when found preponderating in secondary growths in bones, led Cohnheim and others to speak of benign metastasizing goitre

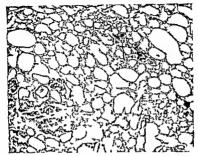


Fig. 295—Well differentiated colloid vesicular structure in a pulmonary metastasis of thyroid careinoma from a man aged 69 (× 60)



Fig. 296 — From a lymph nodal metastasis of cystic papillary adenocarcinoma in a woman aged 81 $\,$ (x 120)

- (b) Non colloid acinar adenocarcinoma of variable degrees of differentiation often accompanies (a)
- (c) Papillar) adenocarcinoma often cystic and often associated with colloid

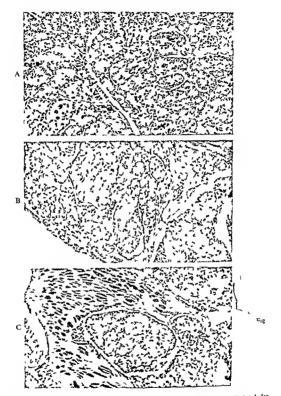


Fig. 299—Case II. Caremoma of lingual thyroid. A = large-cosmophil-celled tubular structure. B = clear-celled structure. C = smaxion of lingual muscle. (\times 100)

but there are also malignant members of the group which recur or metastasize (Haagensen Martin and Elkin) Most of the tumours have appeared in adults but Symmers saw a congenital one. The tumour of the lingual thyroid in Case II below was partly of large cosmophilic celled type.

Many writers from Langhans onwards, described large celled alveolar tumours of the thyroid, and several different hypotheses were advanced ascribing a special histogenesis to them some even supposing them to be of parathyroid origin A resemblance between the large eosinophilic cells of the tumours and the interfollicular cells described by the histologist Hurthle in 1894, led some pathologists to adopt the eponymic name now in current use. This is trebly unfortunate—first, because there is no real evidence that the tumours are related to the cells described by Hurthle secondly, because the very existence of special interfollicular cells in the thyroid is doubtful (Joll) and thirdly because, even if special cells of this kind exist and the tumours arise from them the eponymic name is inappropriate since Baber described the same cells 17 years before Hurthle (see Nonidez, and Wilensky and Kaufman)



Fig. 298 - Large-cosmophil-celled (Hurthle-cell) tumour (x 120)

These large eosinophilic celled adenomas and adenocarcinomas of the thyroid almost certainly arise not from any special source but from the ordinary thyroid epithelium and constitute only one of the many structural variants of which its tumours are capable. Tumours with this structure predominant appear to the naked eye as well circumscribed solid homogeneous opaque white or yellow growths and consist microscopically mainly of large eosinophilic finely granular or foamy polygonal cells arranged in solid trabeculae or around small acinar spaces (Fig. 298). Some tumours show extensive areas of clear celled structure like that of renal adenocarcinomas which indeed can be closely simulated, and as Wilensky and kaufman noted parts of the tumours may show the more usual structural variants of thyroid earenomas. Many of the tumours are beingin in that they grow slowly are well circumscribed and do not recur after removal

(a) Metastases in lymph glands

Regional lymph nodal metastases are common from infiltrative growths, whether of papillary or anaplastic types, but they are often long delayed or absent in cases of "malignant adenoma" in which the tumour is still largely confined within the adenoma capsule. The following case exemplifies metastasis to the regional glands from papillary adenocarcinoma.



Fig. 300—Case III Cystic papillary adenocarcinoma metastatic in a lymph gland Arrows point to calcified spherules colloid vesicles are marked X (× 100)

Case III (Mr Balcombe Quack x case)—In November 1936 a man aged 34 first noticed 1937 enlarged axiliary lymph glands were excised and found to contain cysts filled with colloid and lined by simple cuboidal epithelium further enlarged glands slowly developed and in February 1939 several cervical glands containing cysts filled with brownish fluid were removed and found microscopically to show papillary adeno carcinoma of thyroid origin metastatic in lymph glands (Fig. 300). In view of this report left hemithyroidectomy was performed although the gland was not palpably enlarged more glands in the anterior triangle were also removed. The thyroid was found to contain an ill-defined area of scirrhous adenocarcinoma 15 centimetres in diameter which was quite impalpable and invisible from the surface of the gland. The thyroid was found to contain an ill-defined deposits of papillary growth similar to that removed earlier. In March and April the posterior triangle and axilla were explored and cleared of glands some of which contained deposits of similar growth. Deep X ray therapy was begun in May and the patient remained well at the end of 1939.

'Lateral aberrant thyroids —Do they exist or are they always metastases in the cervical lymph glands from small unsuspected primary carcinomas of the thyroid? This question raised by cases like the foregoing has been discussed by Tebbutt and Woodfull Dunhill Crile, Frantz et al and King and Pemberton In many of the supposed cases of "lateral aberrant thyroids", the authors have

(5) Carcinoma of the lingual thyroid

Wapshaw has reviewed the few recorded cases of carcinoma of the lingual thyroid and the following case exemplifies this rare condition

Case II (Mr. A. F. Maclure's case.)—A man of 26 complained of difficulty in swallowing for several months. Examination showed a rounded slightly lobulated sub epithelial mass 5 centimeters in diameter in the base of the tongue. In this was excised with some difficulty because it infiltrated the muscle at its margins. It consisted of solid white tissue Microscopically (Fig. 299) it presented solid masses and trabectulae or irregularly hollow tubules of large epithelial cells most of which showed solid cosmophilic cytoplasm while others were vacuolated and empty in appearance no colloid-containing vesicles could be found. The lumour subsequently recurred and proved fatal but details are not known.

(6) Function in thyroid carcinoma

Since other ductless glands are the sites of hypersecreting tumours and since parts of many thyroid carcinomas show a high degree of structural differentiation, we might expect signs of hyperthyroidism to accompany many of these tumours. The proportion of cases in which this occurs however is relatively small and the interpretation often far from clear.

In the much quoted classical case of Eiselsberg (1894) total excision of the idenomatous thyroid was followed by signs of sub thyroidism subsequently netastatic adenocarcinoma developed in the sternum and the sub-thyroid toms improved, excision of the sternal tumour was followed by return of ymptoms. later still a tumour developed in the scapula but without further ne improvement. Mori collected the older literature of associated thyroid ma and signs of thyrotoxicosis Pemberton found that in one third of with malignant thyroid tumours, the basal metabolic rates were above In Friedell's series hyperthyroidism was diagnosed in 57 of 412 adenocarcinoma (13 8 per cent) this was more frequent with well differ d than with poorly differentiated growths and with non papillary than papillary ones From Friedell's findings it appears probable that hyper tion by well differentiated adenocarcinomas indeed contributes to the hyperoid symptoms But the question is complicated by the frequent presence of rous changes in other parts of the cancerous thyroids these parts may be ainly to blame for the thyrotoxic symptoms which may be appravated as the result of invasive effects and pressure or vascular disturbances occasioned by the carcinoma There is no evidence that the thyrotoxic thyroid is particularly predisposed to tumour formation reports of patients with exophthalmic poitre later developing carcinoma are rare

(7) Growth and metastasis

No other kind of carcinoma shows a wider range of rate of growth and metastatic behaviour than thyroid carcinoma. At the one extreme, there are the very indolent highly differentiated cystic papillary growths which metastastic to the neighbouring cervical lymph glands and spread slowly from gland to gland over a long period of years—at the other extreme there are the highly anaplastic sarcoma like growths which grow quickly to a huge bulk or disseminate rapidly and widely by the blood stream.

the blood stream, multiple metastases in lungs or bones commonly appear before the cervical lymph glands are affected, and often these metastases are the first signs of disease

Metastases in bones occur in at least one third of all fatal cases of thyroid careinoma. They are most frequent from malignant adenomas", and the structure of parts of the skeletal growths is often highly differentiated and thyroid like. Of course, Cohnheim's concept of "benign metastasizing goite" has now only historical interest, as Berard and Dunet, Joll, Bell, Simpson and others showed, adequate examination of metastasizing thyroid tumours will always reveal ample structural evidence of carcinoma. The skeletal metastases of thyroid

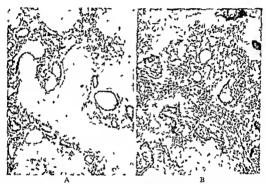


Fig. 301—Mixed turnour from a dog showing closely mingled glandular ussue and ossifying and cartrlagmous (issue A is from primary turnour in thyroid B from an extension within a large thyroid very (x 70).

carcinomas sometimes pulsate, as in the case which Rosenthal and I described, and pulsating metastases have been mistaken for ancurysms (Halbren, Rhea) For other details regarding metastases in bones and diagnostic errors caused by them, see Eiselsberg Gierke Jolf (1923) and my 1934 work

MIXED TUMOURS OF THE THYROID

Not uncommonly in dogs but rarely in man, there occur mixed tumouts of the thyroid containing both thyroid epithelial tissue and neoplastic mesenchymal tissue usually osteogenic or cartilaginous. Funkenstein (1903) reviewed the five previous reports (Zahn s and Pick s) of such tumours in both dogs and man, and described two muligiant ostic chondro sarcomas arising in human goitrous thyroids. He supposed the thyroid tissue which was present in these to be only included residues of gottrous tissue, for in his first case, as also in

remarked on their proneness to low grade papillary growth, their multiplicity their association with lymph glandular tissue and the frequent enlargement of the corresponding lobe of the thyroid Crile, reporting 13 cases of 'papil lary tumors of lateral aberrant thyroids, noted of nearly one half of the cases that the corresponding lobe of the thyroid contained similar growth, yet he concluded that the tumours are essentially beingn 'and that it is probable that many cases reported as papillary carcinoma of the thyroid with metastasis to the regional lymphatics are in reality beingn papillary lateral aberrant thyroids with a coexistent beingn tumor in the thyroid gland. Crile's conclusion that lateral thyroids are essentially beingn is markedly at variance with the findings of all other writers on this subject. For example Frantz et al in 30 cases of lateral thyroid concluded that these showed malignant properties in 23

patients, 8 of whom had died of the disease

From Case III ahove and several similar cases I have seen and from my study of the literature, I think that the evidence fully warrants King and Pemberton's conclusion that so called lateral aberrant thyroid tumors are nearly always metastatic extensions to the deep cervical lymph nodes from a primary carcinoma in the homolateral lobe of the thyroid gland. I had come to the same conclusion before I read King and Pemberton's excellent paper, and I would go even further and say that there is no evidence that developmentally aberrant thyroid tissue ever occurs in the lateral position. Sir Arthur Keith who has had a wide experience of developmental anomalies of the head and neck, informs me that he has never seen or read of an unequivocal instance of the presence of a mass of detached normal thyroid in the lateral position. A 'lateral aberrant thyroid calls for hemithyroidectomy and if this is done a small carcinoma will always be found, if searched for in the excised lobe.

The following ease also recorded elsewhere (Willis 1941 Case 441) exemplifies not only diagnostic difficulty caused by metastases in lymph glands but also the

wide variety of structure which a thyroid carcinoma may show

Case IV—History—A woman of 62 was admitted to hospital with a mass 10 centimetre in diameter notused enlarging for 3 weeks in her right actilla. This was increased as an abscess no pus was found and a piece of tessue which, was removed showed a rapidly growing round-celled turmour thought to be a sarrorma. Accrops 4 weeks later showed that although the thyroid was not enlarged its right tobe was replaced by soft white growth microscopically showing diffuse round-celled growth ket hat from the willabut with aniar formation in places. Multiple metastases were present in the cervical and avillary lymph glands and in the lungs and kidney. The vertex of the skull showed a small area of erosion microscopical examination of which showed well formed colloid containing thyroid vesicles. No other skeldstal metastases were found.

(b) Blood borne metastases

In a high proportion about three quarters of latal cases of thyroid carcinoma metastases are present in lungs, other viscera or bonne. The source of haemic dissemination is often demonstrable veins invaded by growth can frequently be found microscopically in the primary tumours especially in malignant adenomas or their capsulus (Ethrhardt Erdheim Graliam Warren Dunhill) Sometimes the tumours grow massively into large thyroid veins and extend into the jugular and innominate veins and even into the right attrium (Carrington, Shepherd, Wylegschann) Malignant adenomas metastasize principally by

kinds of heterotopic tissues, these are teritomas (see Chapter 61). It is probable that in Zahn s first case (cited by Funkenstein) the tumour was teratomatous and not related to the tumours just discussed, for it contained not only cartilage and glandular tissue but striated musck fibres also, and it was found in a 7 months foetus

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Zahn s and Pick's cases metastatic growths consisted of sarcomatous tissues only and were devoid of epithelial elements. Ewald reviewing 80 malignant tumours of the thyroid in dogs found 7 mixed tumours. Chavannaz and Nadal concluded that the thyroid epithelium in these growths is truly neoplastic and that the malignancy of the tumours is total involving all components. The findings in a dog tumour which Rudduck and I reported (Figs. 301 and 302) supported this view for an invaded large vein contained both osteosarcomatous and epithelial components of the growth.

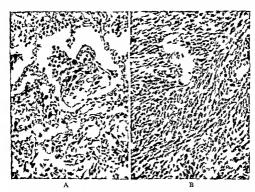


Fig. 302 — From pulmonary metastases of the tumour of Fig. 301. A = osteosarcoma with plentiful osteoid tissue extending within lung alveoli. B = spindle-cell sarcoma with a focus of early osteoid differentiation (x. 240)

malignant tissue however was shown by the fact that multiple metastases in the lungs consisted of it alone without any epithelial elements as in the case of Funkenstein and others. As far as I know no case has yet been reported in which metastases have been of mixed structure. thereby proving beyond doubt the

total malignancy of the tumours Specimens of mixed tumour deserve still more thorough study in order to settle this point and in any occurring in dogs or other animals an attempt to transplant the tumours and to segregate their components might lead to informative results just as it has done with the mammary mixed tumours of rats

The osteosarcomatous or chondrosarcomatous mixed tumours of the thyroid appear to form a distinct and peculiar group arising in gottrous adult glands and associated with hyperplastic or neoplastic thyroid epithelium Unrelated to these are some other reported mixed tumours of the thyroid containing other

CHAPTER 37

EPITHELIAL TUMOURS OF THE THYMUS

INTRODUCTION

CONFUSION still prevails regarding the nature and classification of thymic tumours, the reasons being mainly two, namely (a) doubts in the minds of some writers regarding the origin of the small thymic cells, whether these are immigrant lymphocytes or special cells derived from the thymic epithelial reticulum, and (b) the great number of mistaken diagnoses of 'thymic tumour' in cases of pulmonary and other non-thymic growths with anterior mediastinal extensions. Brief discussion of these two sources of confusion is called for

(1) The histogenesis of the small cells of the thymus

Is the small thymic cell a lymphocyte or an epithelial derivative? If the former, then we must clearly distinguish between lymphoid tumours and epithelial tumours of the thymis. If the latter, then the so called lymphoid tumours ('lympho sarcomas', cte) of the thymis are not lymphoid at all and the round celled and epithelial celled growths are akin and can all be grouped together as "thymomas". In my opinion, the study of thymic tumours confirms the opinion of most embry ologists and histologists and shows conclusively that the small round cells are lymphocytes intimately admixed with the opithelial reticulum of the organ or its tumours. The tumours show all degrees of such admixture, and all degrees of segregation of the two components. The term "thymoma" is only a means of escape from the practical difficulty of distinguishing microscopically between the more cellular diffuse lymphocyte-containing carcinomas and the relatively rare true lymphosarcomas of the organ.

The thymus is of course not the only organ the tumours of which have presented this difficulty so also have some of those of the tonsil and other parts of the pharynx, organs to which the thymus is closely related developmentally From all of these, arise carcinomas characterized by an abundant admixture of lymphocytes with loosely textured or diffuse epithelial growth-the so called "lympho The lymphocyte rich thymic carcinomas are identical in structure and behaviour with their nasal and pharyngeal counterparts. Hence, in theory at least, we must distinguish sharply between true lymphoid tumours whether arising from thymic lymphocytes or from neighbouring lymph glands, and In practice this may carcinomas arising from the thymic epithelial reticulum sometimes be difficult an occasional highly anaplastic lymphocyte rich "lympho epithelioma may easily be mistaken for a lymphoid tumour. In general diagnoses of thymic 'sarcoma' are probably about as reliable as those of pharyngeal sarcoma" Many growths which were once called "lymphosar of the tonsil or pharynx are now recognized correctly as anaplastic carcinomas of lympho epithelioma type From a perusal of the literature, there is no doubt that the same mistake has frequently been and is still being made regarding thymic tumours, many of the supposed "sarcomas" are really

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(3) Thymic tumours in animals

Curtis et al recorded a high meidence of thymic tumours in a colony of rats, the tumours occurred in only one strain of animals, affected females more often than males, and were usually benign but sometimes malignant Ratcliffe also observed thymic tumours in rits Feldman saw a carcinoma of the thymus in a ewe, and Orr saw one in a rabbit

PERSONALLY STUDIED CASES OF THYMIC EPITHELIAL TUMOURS

I have studied 3 necropsy cases of thymic tumour in which the diagnosis is established beyond doubt. These serve to show the range of structure and behaviour of this group of tumours

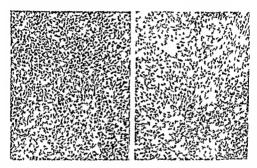


Fig. 303 - Case 1 Diffuse thymic carcinoma with many admixed lymphocytes (x 100)

Case I ~ A female infant aged I year had shown recent general debility and anaemia with enlarged spleen and enlarged cervical axillary and inguinal lymph glands. Blood examination excluded leukaemia. Necropsy—Large thymic tumour (70 grammet) enlargement of many groups of lymph glands by tumour deposits diffuse and nodular tumour infiltration of spleen (310 grammet). All other viscera and bone marrow free from growth. Histology (Fig. 303)—Growths in thymus glands and spleen all show similar structure consisting of large polyhedral and irregular epithelial cells of diffuse reticular arrangement with some poorly formed whorls with many mitour figures patchy infiltrations of lymphocytes partly focal and partly diffuse immgled with the epithelial reticulum throughout large areas of necrosis present in places. Comment—in briefly recording thus case previously (Willis 1934) htthough I classified it provisionally as a thymic carcinomia with metastases I suggested also the possibility of its being some kind of systemic neoplasta affecting thymus glands and spleen similianeously. Further study in the light of other published cases however fully convinces me that the tumour was indeed a thymic carcinomia.

Case II—History—In October 1936 a man aged 47 professional athlete, was admitted to hospital because of severe left precordal and epigastic pain of 6 days duration worse on exertion and accompanied by dyspnoes takingtams showed right basal pleural effusion and enlargement of heart shadow with a large oval projection on

diffusely cellular carcinomas with admixed lymphocytes and genuine primary lymphosarcoma and other sarcomas of the thymus are very rare

(2) Mistaken diagnoses of 'thymic tumour'

This second cause of error is even more serious than the first. It cannot be too strongly insisted that the diagnosis of thymic careinoma can be made with confidence only when careful necropsy examination has excluded the possibility of the mediastinal mass being secondary to some other growth requirement has so often been ignored, that many otherwise carefully recorded series are rendered valueless for analysis of the properties of thymic growths For example Symmers recorded that in 10 of his 25 supposedly thymic tumours the larger bronch; were buried in tumor tissue, and that in many cases the bronchial walls were infiltrated and their lumina encroached on also Parabutschew, though insisting that the diagnosis of thymic carcinoma necessitated exclusion of the possibility of a primary tumour elsewhere reported as thymic in origin two cases (his second and fourth) in which the lungs were extensively involved and might easily have been the primary source of the growths Crosby's tabular summary of recorded cases of thymic tumour shows how frequently the lungs are reported to have been involved secondarily direct reference to many of these cases confirms the suspicion that the primary source and direction of spread may well have been misinterpreted

Clearly, of course malignant thymic growths are likely to invade the lungs and it is not intended to deny that some of the recorded tumours with extensive involvement of the lungs may indeed have been thymic in origin. But clearly, involvement of the lungs necessarily introduces room for doubt regarding the primary source of the tumour and the more extensive this is and the more elosely it is related to bronch; the greater is the probability of a pulmonary origin Pulmonary tumours are much commoner than thymic ones they often produce massive lymph nodal or mediastinal extensions and these can arise from yery

small elusive primary growths (see Chapter 19)

It may be argued that microscopical study should enable us to distinguish theme from pulmonary and other carcinomas. Certainly some thymic growths have a rather distinctive. Ilympho epithelial structure and this may sometimes afford good evidence of the source of a tumour of otherwise doubtful origin microscopical diagnosis. and the number of tumours in which it will be possible to do so must be small. In most cases confident microscopical distinction between thymic carcinoma and poorly differentiated epidermoid or other anaplastic carcinomas of the lungs will not be possible.

For the foregoing reasons many of the recorded eases of 'thymic carcinoma (or thymic sarcoma) are suspect even though some of them may have been genuine enough. Hence no trustworthy analysis of age or sex incidence or other properties is at present possible. The number of unimpeachable cases so fair recorded is too few to permit generalizations. For useful accounts and references, see Parabutschew Margolis Crosby and Wu. (The thymic tumours associated with myasthema gravis or with endocrine disturbances are referred to separately below.)

4th and 9th dorsal and the 3rd and 4th lumbar vertebrae contained some irregular areas of soft white or mottled growth. Naked-eye necropsy diagnosis was '? cystic antenor

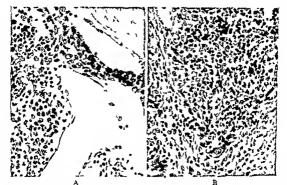


Fig. 305—Case II Structure of carcinoma A—well defined epithelial clumps containing scattered lymphocytes B = diffusely mixed carcinoma and lymphoid cells (× 300)

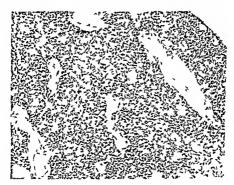


Fig. 306—Case III Typically epithelial growth with whorls and scattered lymphocytes (v 120)

mediastinal teratoma old teratomatous metastases in left pleura recent malignant degeneration with metastasis to lymph glands liver and bones Histology (Figs. 364 and 305).—The cavities in the mediastinal and pleural tumoura are lined irrigularly by its inght border—7 neoplasm Discharged improved in December he was tradimited in January 1937 because of another similar attack no noteworthy changes in physical signs or radiographic appearances diagnosis coronary occlusion—again discharged improved. Patient then remained well until August 1940 when he had an attack of pneumonia. In Oxtober he began to suffer from pains in neck chest and left arm and from increasing dyspinoea hourseness and feeling of pressure in chest. Admitted to hospital in February 1941 he was found to have visible anterior bulging of upper part of sternum a large area of duffiness to percussion enlarged superficial veins and right besalt duffiness. Skiagrams showed large anterior mediatinal timours—2 hydratids. Died in March 1941. Wergers—Anterior mediatistium occupied by large well defined roughly



Fig. 304 — Case II Cystic carcinomatous masses separated by thick densely fibrous septa $(\times 80)$

wedge-shaped but lobulated mass 12 centumetres in transverse diameter 10 centimetres vertically and 4 centimetres in maximal thickness at its upper end displacing sternum forward overlapping both lungs and basal half of pericardium which were adherent to but not invaded by the growth. This was very hard and on section consisted of small and large pregular cavities up to 3 centimetres in diameter. I med only here and there by a thin layer of white fumour tissue and occupied mainly by fibrinous material or blood stained fluid and separated by thick irregular partly calcified partitions continuous with the main capsule of the growth. A bulging lobule of the growth projected towards the hilum of the right lung but without invasion of lung tissue. All bronchi normal. Left pleural cavity contained 5 discrete well-defined encapsulated hard cystic masses similar in structure to main growth situated as follows (a) at aper a discoid mass 10 centimetres in main diameter adherent to apex of lung upper ribs and deep tissues of neck (b) rounded tumour 9 centimetres in diameter in lower lateral part of pleural cavity (c) a smaller rounded tumour close to preceding one (d) interlobar in position (e) between base of lung and diaphragm Lymph glands near angle of trachea were enlarged and contained soft white growth unlike that of the thymic and pleural tumours. Liver contained several small scattered soft white or greyish metastases the largest 2 centimetres in diameter All other lymph glands viscera and brain were carefully examined and no growths found A small peptic ulcer was present in the stomach a heated scar in the duodenum and adrenals showed some nodular cortical hyperplasia. The dura and bone of the right border of the foramen magnum presented a projecting mass of soft prevish tumour. The

tissue admixed with lymphocytes, the epithelium being most disorderly and diffuse in Case I and most compact and well differentiated in Case III The three tumours are in fact "lympho epitheliomas" of descending order of anaplasia and malignancy The structural variations displayed show clearly that the epithelium is the essential tumour parenehyma and that the lymphocytes are immigrants unrelated genetically to it. The lymphocytes are of patchy distribution. of very variable proportions in different parts of the growths, and often most plentiful in perivascular tissues as if they had collected in the tumours in response to some lymphocyte-attracting property of the epithchium, a property which we would expect to vary from part to part of a tumour according to the differentiation and growth properties of its cells. The absence of cornification in the three tumours is noteworthy, this accords with the findings of most other workers, squamoid characters in the tumours are often restricted to the formation of cell whorls or groups of cells resembling Hassall's corpuscles Case II strikingly exemplifies both the cystic tendency of thymic carcinoma, and the great stromal proliferation which the more chronic forms of growth induce

(2) Behaviour

Cases I and II exemplify metastasis both to lymph glands and by the blood stream to remote viscera and bones. In addition, Case II illustrates the slow progress of some thymic carcinomas, and also the unusual phenomenon of trans pleural transplantation of a very chronic tumour. Danisch and Nedelmann saw a thymic tumour in a child of 3½ years the structure of which resembled that of my Case I but with a higher proportion of lymphocytes, and which invaded the innominate vein and metastasized widely to the choroid pleus, meninges, heart wall and kidneys, as well as to the cervical lymph glands. The absence of invasiveness or metastasis in my Case III leads us to a brief discussion of the thymic tumours associated with myasthenia gravis.

THYMIC TUMOURS IN MYASTHENIA GRAVIS

Thymic enlargement in myasthenia gravis was first described by Carl Weigert in 1901 (cited by Bialock et al, 1939). In 1917, Bell collected 56 records of cases of myasthenia gravis in which necropsy or operation had been performed, 27 of these had thymic abnormalities, described as tumours in 10 cases and as persistence or simple enlargement of the thymis in the remainder. Norris (1936 and 1937) and Blalock et al. (1939 and 1941) have reviewed later records. Norris at first inclined to the view that the lesson was hyperplastic only and not a true tumour, but later modified this opinion and concluded that it was an "adenoma." The size and structure of the growth in some reported cases (as my Case III) indicate true tumours, but in other cases (e.g. those of Blalock et al. 1941) there has been simple enlargement only. All of the tumours reported have been benign no definite case of associated careinoma of the thymus and myasthenia has been reported. The beneficial effect on the myasthenia of removal of the tumour has been well established, but the precise relationship of the two still remains obscure.

THYMIC TUMOURS AND ENDOCRINE DISTURBANCES

Although there is no clear evidence that the thymus produces an internal

compact or loosely reticular epithelium of stratified type but without cell nests or comification intoses few Pfentiful lymphocytes migle with the epithelium in varying proportions. The ramifying epithelial masses and cysts are embedded in and separated by bulky densely fiftrous septa in which much cledication and some ossification have taken place. Mictastases in lymph glands liver and bones show spheroidal-cell carcinoma with many mitoses. Irmphocyte militration though present in parts is much less abundant than in the thymic and pleural tumous. Beginssis and comment—The histology establishes the diagnosis of thymic carcinoma of lympho epithelial type the neoplastic epithelium is similar to that of many plaryingeal tumous. Remarkable are the long duration (at least 44 years probably much longer) the extreme cystic change in the older growths the great stronal fibroses evoked by these the metaplastic ossification of stroma and the two distinct kinds of metastases namely those in the left pleura of the slowly growing cystic type with great stromal fraction as in the primary growth and those in



Fig 307 -Case III Details of epithelial whork seen in Fig 306 (x 250)

the sudden severe but evanescent attacks of thotacce pain in 1936 were due to rupture of part of the cystic thymic tumour into the left pleural cavity whence arose the peculiar unlateral metastases of relatively benign type like the parent tumour. The more recent dissemination to viscera and bones must be attributed to an exacerbation of growth rate and mafignancy in some part of the primary growth.

Case M—Necropiy (Dr. E. H. Derick) on an emaciated man of 39 years who had had symptoms of myasthenia gravis for some years disclosed a firm well-defined nodular thymic tumour $5 \times 5 \times 2.5$ centimeties weighing 34 grammes composed of grey or haemorrhagic tis, we with spongy finely cystic areas enclosed in fibrous capsule and trabeculae. Histology (Figs. 306 and 307)—Bulk of tumour is composed of large masses of epithelium separated by vascular fibrous stroma. Epithelium is of stratified type and contains some small whords but shows no comfication. Most of it is compact but other parts are loosely relicular or contain many small spaces. Mitoses in tumour cells are very few. Infiltrations of lymphocytes are present in all parts most plentiful in the pervascular stromal tissue and mingled with the reticular areas of epithelium.

COMMENTS ON FOREGOING CASES

(1) Structure

The three tumours have this in common-they all consist of an epithelial

CHAPTER 38

EPITHELIAL PITUITARY AND PARAPITUITARY TUMOURS

EPITHELIAL tumours of the pituitary gland and of the developmental residues associated with it can be conveniently grouped as follows

- Group 1 Tumours of the secreting tissue proper
 - Benign adenomas
 - (a) Chromophobe
 - (b) Eosmophil
 - (c) Basophil
 - (d) Mixed
 - 2 Carcinomas
- Group 2 Tumours of the parapituitary residues
 - Simple cysts
 - 2 Squamous cell carcinomas and "adamantinomas"

Good general accounts with many references, include those of Strada (1911) and Erdheim (1925) Cushing's monograph (1912) and Dott and Bailey's paper (1926) are major contributions to the subject Biggart and Dott (1936) have given a useful brief summary

PITUITARY ADENOMAS

The non invasive tumours of the pituitary secretory tissues are all appropriately called adenomas. Their structure and their all but constant intrasellar situation show that most of them arise from the anterior lobe, but though difficult to prove, it is probable that occasional tumours may arise from the epithelium of the pars intermedia or of the pars tuberalis. According to the staining properties of their cells, three main types of adenomas are distinguished—chromophobe, cosmophil and basophil, but this distinction is somewhat arbitrary, since tumours of mixed type occur. Pituitary adenomas occur mainly in young and middle aged adults, they rarely appear in patients under 20 years of age or in the elderly

(1) Chromophobe adenoma

This group comprising about two thirds of all pituitary adenomas, includes all adenomas the cells of which show non distinctive staining properties. The growths are of very diverse structure. Some of them consist of trabeculae of polyhedral cells with intervening stroma and vessels, closely simulating the general structure of the normal gland. Others depart from this in various ways presenting reticular patterns, prominent perivascular mantles of cells elongated cells, or areas of pale cells with vacuolated cytoplasm. Elsewhere (1938) I have depicted examples of these variations, and have stressed the structural diversity of the group Mitoses are infrequent, but no sharp separation can be made between the common benign tumours and the rarer malignant ones showing anaplasia. Invasiveness

secretion certain nathological observations suggest some relationship of thymic and endocrine functions. On the one hand thyrotoxicosis is often accommanied by thymic enlargement and on the other hand rare cases of thymic tumour or enlargement have shown marked endocrine disturbances. Thus Levton et al. fully described the necronsy findings in two patients with thymic tumours. one in a boy of 11 years who had had hirsutism and diabetes, the other in a man of 31 with admostly and diabetes, both cases showed also enlargement of the thyroid and adrenal cortex. Dueund and Kennedy saw a thyrnic tumour accompanied by similar endocrine disturbances in a woman of 64. Parkes Weber described a case of precocious muscular and sexual development in a boy who had also an extensive unilateral pigmented naevus and X ray evidence of marked thymic enlargement later, however, this boy developed normally. and the enlarged thymic shadow in skiagrams disappeared

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and 1933) that these growths were the essential cause of a syndrome which he designated 'pituitary basophilism' and which is often referred to as "Cushing s syndrome, is now untenable. The syndrome itself is very variable and often imperfectly manifested by patients with basophil adenomas (Russell et al.), and identical syndromes are found in patients with adrenal cortical tumours and without printiary adenomas (references in Chapter 39). Hence, while it is true that basophil adenomas of the pituitary are found in many cases showing the symptoms of Cushing's syndrome, all of these symptoms cannot be directly attributed to hypersecretion of basophil cells. It is probable that the condition is a polyglandular disturbance in which both pituitary and adrenal glands are implicated. Further careful necropsy and experimental work is needed to deter mine which of the many and variable symptoms included in the syndrome are related to pituitary dysfunction and which to dysfunction of the adrenal coxtex or other ducites glands.

(4) Growth and behaviour of pituitary adinomas

Most pituitary adenomas grow slowly and non invasively. In their early stages they are often not encapsulated, and it is probable that they commence as focal hyperplasias which go on to tumour formation a sequence similar to that observed more clearly in the thyroid gland. Since adenomas are with rare exceptions intrascilar growths they usually cause early enlargement of the pituitary fossa and early compression and hypofunction of the remainder of the gland. Bulky tumours expand and project through the daphragma sellica into the cranial cavity, where they compress the optic chiasma and tracts, indent the hypothalamic region or mid brain fill and distend the third ventricle, and even extend through the foramina of Monro into the lateral ventricles. They may also project into and distend the sphenoidal and insal cavities. Large tumours often show cystic and degenerative changes. Striking examples of expansive extension will be found in Strada's Erdheim's and Cushing and Davidoff's studies. Invasive growth or metastasis places the tumour in the malignant group now to be discussed.

CARCINOMAS OF PITUITARY GLANDULAR TISSUE

Some pituitary tumours must be classified as malignant because of local invasive spread or, more rarely, metastasis by the cerebrospinal fluid or blood stream. But these tumours are not sharply separable from the common non invasive denomas they are merely more aggressive members of the same species.

(1) Anaplasia and invasive spread

When a pituitary tumour invades the neighbouring dura bones and sphenoidal sinus as in two cases which I reported in 1938 it may be difficult or impossible to be sure that the growths are indeed of pituitary origin and have not arisen in the sinus or other neighbouring parts. However the whole of the evidence pointed to a pituitary origin in my two cases, and indubitable instances have been described also by Stradi. Dott and Bailey and others. One of my specimens from 1 girl of 14, showed a seminoma-like structure with ill defined groups of large spheroidal

and plentiful mitoses (see belon) Chromophobe adenomas produce no symptoms attributable to secretory activity of the tumour cells their usual endocrine results are due to diminished pituitary functions or to compression of neighbouring structures. They often attain a large size

(2) Eosinophil adenoma

Tumours consisting wholly or partly of eosinophil cells with characteristic granules and producing excessive growth hormone constitute about one third of the pituitary adenoma. Acromegaly or acromegale gigantism is probably always due to eosinophil adenoma and predominantly eosinophil cell adenomas always produce acromegaly. Predominantly chromophobe cell tumours may however, contain a few cosinophil cells without producing obvious acromegalic changes

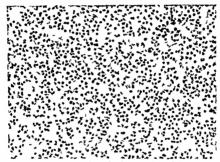


Fig. 308—Pituitary adenoma composed entirely of eosinophil cells from a man aged 42 with advanced acromegaly (× 180)

It is clear that cosinophil and chromophobe adenomas are not sharply distinct types but merely variants of the one kind of fumour with greater or lesser degrees of cellular differentiation and production of growth hormone. Microscopically most of the cosinophil cell growths show a general structure closely similar to that of the normal tissue and with varying proportions of cosinophil cells in some cases all of the cells are cosinophil (Fig. 308). The tumours sometimes attain a large size but on the average they are smaller than chomophobe adenomas For the clinical and pathological changes of acromegaly and gigantism see Cushing and Davidolf Narges and Laurie

(3) Basophil adenoma

Basophil cell adenomas are rare and small seldom exceeding a few millimetres in diameter and sometimes being almost microscopic Biggart and Dott mention having seen a specimen 2 centimetres in diameter Cushing 5 original view [1932] body of the sphenoid, in the capsule of the pituitary gland especially of its anterior lobe, in the pars intermedia and around the infundibulum. The "pharyngeal pituitary gland" which is present in nearly all subjects (Haberfeld, Christeller, Melchionna and Moore), and the occasional epithelial residues in the body of the sphenoid, are rarely the site of tumours. But the abundant residues in the pituitary capsule and infundibulum, found in about one third of adults (Carmichael, Susman), not infrequently give origin to cysts and tumours, which have often been lumped together under the unsatisfactory name 'craniopharyngioma' Most of these cysts and tumours arise from the suprasellar residues, but some arise from those within the pituitary fossa. For good accounts see Critchley and Ironside, Erdheim, Frazier and Alpers (1931) and Frazier



Fig. 310—Wall of a pituitary cyst lined by ciliated epithelium found at necropsy on a woman aged 29 with Frohlich's syndrome (× 450)

(1) Simple cysts of the parapituitary residues

These need not concern us in detail here They are usually lined by squamous stratified epithelium, in contradistinction to intraptituitary cysts lined by columnar ciliated epithelium (Fig 310), which are believed to arise from Rathke's cleft in the pars intermedia (Frazier and Alpers, 1934). Frazier, 1936)

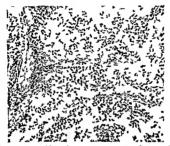
(2) Tumours of the parapituitary residues

These are not distinct kinds of growth, and the improper term "adamantinomas' means no more than that tumours of the parapituitary residues often closely resemble in structure those of the paradental residues (Compare Figs 311 and 312 with Figs 130–132 of Chapter 16). This resemblance is not surprising considering that both sets of residues have a closely similar developmental origin and consist of closely similar foci of indifferent epithelium. Like their paradental counterparts also parapituitary adamantinomas' occur in relatively young subjects. Of 18 cases described and reviewed by Critchley and Ironside, 7 were in the second decade and 6 in the third, the voungest patient was 7, and the oldest 60 years of 14 cases studied by Frazier and Alpers 9 were between the ages of 7 and 17 and the ages of the remaining 5 patients were 25, 28, 33 38 and 50. I have examined 4 specimens of parapituitary "adamantinoma" from patients aged 10. 14. 24 and 28. One of these, from Case XIX of my 1938 paper, is depicted in Figs 311 and 312. These slowly growing tumours are often cystic and calcified,

tumour cells with many mitoses accompanied by scanty stroma with collections of lymphocytes (Fig. 309)

(2) Cerebrospinal metastasis

Cerebrospinal dissemination of a pituitary tumour was recorded by Cagnetto, although the necropsy was incomplete, this interpretation was probably correct Cairns and Russell briefly mentioned a case of bulky pituitary admonas in which peculiar cells had been observed in the cerebrospinal fluid during life and in which necropsy revealed scattered cells in the spinal meninges but without gross tumour formation.



Fio 309 - Anaplastic seminoma like malignant pituitary tumour from a girl aged 14 (reported in 1938) (× 85)

(3) Blood borne metastases

These are very rare Budde's ease of spheroidal-cell carcinoma with metastases in cervical lymph glands lungs and pleura was probably but not certainly of pituitary origin. Dott and Bailey neutoned a necropsy case of pituitary carcinoma with metastases in liver and lymph gland but gave no details. Vasiliu's diagnosis of primary pituitary tumour in a case showing a large mediastinal growth and many metastases in hones cannot be accepted it is much more likely that the small pituitary tumour was metastatic and that a primary carcinoma of the lung escaped detection. Similarly Gilmour's case of carcinoma of the pituitary gland with abdominal metastases was more probably one of primary abdominal—perhaps renal—carcinoma with a pituitary metastasis. Forbes has reported a convincing specimen of carcinoma of the anterior pituitary labe with metastases in the liver.

THE PARAPITUITARY RESIDUES AND THEIR TUMOURS

Small foci of squamous celled or nondescript epithelium derived from the stalk of Rathke's pouch are found in the adult in the roof of the nasopharynx, in the

PITUITARY AND PARAPITUITARY TUMOURS IN ANIMALS

Hare described a chromophobe adenoma associated with dystrophia adiposogenitalis in a bitch aged 9 years, and referred to two previous reports of adenomas in horses. White reported a peculiar squamous-cell cystic suprasellar tumour in a male dog of 4 years Great enlargements of the pituitary gland can be produced in rats or mice by prolonged treatment with oestrogens (see Section V. Chapter 4) but it is doubtful if these are true neoplasms, since there is as yet no evidence that they progress after cessation of the treatment Vasquez-Lopez, however, has succeeded in producing large atypical growths with all the appearances of true tumours, by a combination of oestrogen treatment and the administration of either thiourea or acetylaminofluorene

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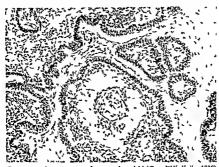
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yet infiltrative and dangerous invading the adjacent bones or brain and frequently recurring after removal. It is not unusual for bone to develop by metaplasia in



Fio 311 —Pituitary adamantinoma from a girl aged 14 (Case XIX Willis 1938) (x t20



Fig. 312 —From the same case as Fig. 311 showing tumour clumps invading nervous tissue in wall of third ventricle. (\times 85)

the stroma of the growths (Erdheim Josephy) Metastasis occurs rarely if ever Garschin reported a large squamous-cell carcinoma of the sphenoid and pituitary fossa which he believed possibly correctly, to have arisen from intrisphenoidal parapituitary residues, and which had metastasized to lung lymph glands and liver

PITUITARY AND PARAPITUITARY TUMOURS IN ANIMALS

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CHAPTER 39

TUMOURS OF THE ADRENAL CORTEX

RENIGN ADENOMAS

SMALL cortical adenomas of the adrenals are frequently discovered incidentally at necropsy. They appear as well circumscribed rounded yellow masses similar in appearance to the cortex of the gland, sracly more than 2 or 3 centimeters in diameter usually single but sometimes multiple. They are found most often in middle aged or old subjects and in women more often than men and they are not associated with any distinct endocrine disturbances. In structure they closely resemble the normal cortex and usually show pronounced lipoid vacuolation of their cells (Fig. 313). Metastatic timours in the adrenal cortex show a decided predilection for adenomas (Willis 1934).

CORTICAL CARCINOMAS OR 'HYPERNEPHROMAS"

The nomenclature of the large progressively growing tumours of the adrenal cortex needs clarification. The term hypernephroma has deservedly fallen into such bad odour because of its frequent misapplication to renal tumours and also to non cortical adrenal tumours that it should be discarded. But to call the tumours carcinomas is to assert their epithelial nature while as pointed out in Chapter 2 histologists are loth to regard the adrenal cortex as epithelial. However cells of the adrenal cortex and its tumours are epithelium like in their general structure and arrangement and most pathologists think of them as epithelial. Hence I can see little real objection to applying the name carcinoma to the tumours. Again no sharp separation of benign and malignant growths is possible whether a large circumscribed but growing tumour shall be regarded as an unusually active adenoma or as a carcinoma' which has not yet displayed invasiveness or metastasis is a matter of personal preference.

Bulloch and Sequiera's paper in 1905 was the first in this country to concentrate attention on the association of adrenal cortical tumours and sexual development. In 1912 Glynn published his classical account of the subject which he amplified in 1921 in a further important paper. Proof of the endocrine activity of the tumours was afforded by improvement in the signs of virilism following surgical removal of the tumours as in the cases described by Holmes (1925) and Murray and Simpson (1927). More recent reviews and general accounts of the subject include those of Kepler. Kepler and Keating. Simpson and Joll Broster et al. and Cahill et al.

(1) Age and sex incidence

No age is exempt—the tumours have been found in infancy and in old age but most patients have been between 25 and 45 years of age—Females are affected much more often than males—and the same sex difference is seen in pre adolescents as in adults—in 1939—Reilly et al. found records of 40 cases in pre adolescent girls while in 1941 kepler and Keating could find only 17 cases in boys

(2) Structure and growth

Many of the tumours have a well differentiated structure closely resembling that of the adrenal cortex. When such tumours are well circumscribed and devoid of metastases and have not recurred after surgical removal, no objection can be raised to calling them adenomas? But tumours of similar structure may recur or metastasize, and distinction between benign and malignant growths is therefore arbitrary. Other tumours, however, are frankly malignant in structure and behaviour, exhibiting varying degrees of cellular anaplasta and invasiveness, and often showing variable differentiation in different parts, some areas being adrenal cortex-like while others show disorderly cellular pleomorphism. These variations of structure are well depicted by Cahill et al. Special cytological details related to the hormonal properties of the tumours are discussed below.

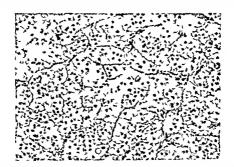


Fig. 313—Cortical adenoma of adrenal gland a solitary spherical turnour 2.5 centimetres in diameter from a woman aged 60 (> 150)

The sizes attained by the tumours vary greatly Some have attracted attention by their endocrine results while still quite small, others have grown to huge sizes without producing noticeable hormonal disturbances. As examples of large tumours may be mentioned the tumour of beingn type accompanied by pronounced virilism removed by Holmes which weighed 1,025 grammes, and the malignant tumour accompanied by only slight hormonal upset, described by Anderson et al., which weighed 1,780 grammes

Examples of fatal recurrence after removal, or metastasis to the lungs, liver or clawhere include those of Mutray and Simpson Hare et al. Simpson and Ioll and Anderson et al. In Femblatt s case a virilizing light adrenal tumour in a woman of 32 had invided the inferior vana cava and extended up to the heart. In Busch's case a man of 27 had gynaecomastia as the first symptom, enlarged left cervical lymph nodes appeared and biopsy of these established the diagnosis.

CHAPTER 39

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(d) Other endocrine changes

Adrenal cortical tumours may produce any of the symptoms comprised in Cushing's syndrome of so called "pituitary basophilism" (Lescher and Robb Smith . Hare et al . Kepler and Keating , Cabill et al) These symptoms include purplish cutaneous striae, raised blood pressure and patchy decalcification of the skeleton, as well as hirsutism and obesity. These changes point to the close interrelationship between the pituitary and adrenal glands, discussed fully by Vines and by Burrows, and they also show that "pituitary basophilism" is not a proper synonym for Cushing's syndrome, a question already discussed in Chapter 38

Hormonal assays of the urme of patients with virilism or feminism due to adrenal cortical tumours have substantiated that these effects are due to excessive production of androgens or oestrogens respectively Patterson et al., Anderson et al., Callow and Crooke, and other workers cited by Burrows have demon strated excess of androgenic steroids in the urine of patients with virilism Burrows et al demonstrated excessive destrogenic hormone in the urine of the feminized male patient described by Simpson and Joll, this excess disappeared after operative removal of the tumour and returned with its recurrence. (See also the discussion following Broster's paper, 1946)

Cytological studies show a relationship between the cellular structure of the tumours and their hormonal activity The fuchsinophil reaction of Vines is strongest in tumours with androgenic properties According to Goormaguigh, the cells of virilizing tumours form siderophil and fuchsinophil granules, those of feminizing tumours do not, but show yellow pigment granules and those of tumours devoid of endocrine effects show neither Ross carefully compared the structure of Simpson and Joll's specimen of feminizing tumour with that of a tumour from a woman with virilism, and found significant differences of cytology and staining properties

Adrenal cortical disfunction without tumour must be mentioned Endocrine disturbances similar to those accompanying tumours can also be brought about by simple hyperplasias or even hyperfunction without enlargement of the glands In many cases of this kind recorded by Broster et al, Vincs found "essential hyperfunction with virilism" to be almost constantly associated with strongly positive fuchsinophil properties of the adrenal cortex, while in cases of Cushing's syndrome the fuchsinophil test was usually negative or only weakly positive

ADRENAL CORTICAL TUMOURS IN ANIMALS

Adenomas or carcinomas of the adrenal cortex are amongst the commonest visceral tumours of cattle, Feldman (1932) saw 19 examples and referred to others and Rudduck and I studied 4 specimens Although these tumours are often large, vascular and necrotic most of them are well circumscribed and devoid of metastases In sheep also, adrenal cortical tumours are one of the commonest forms of new growth Feldman (1931) saw 10 cases, with unilateral tumours in 7, bilateral tumours in 3 animals, although these appeared histologic ally malignant no metastases were present Rudduck and I examined bilateral cortical adenomas from 2 dogs Feldman refers to one recorded instance of adrenal carcinoma in a horse Curtis et al, Ratcliffe Hueper and Ichniowski,

(3) Endocrine results of adreoal cortical tumours

The complexity of this subject can be gauged from a perusal of Pirt VI of Burrows's book on the sex hormones. From the normal adrenal cortex, more than a score of different but related sterol substances have been isolated, some of them androgenic, some oestrogenic some with progestin effects, and some with more general metabolic effects not related to sexual characters. It is then not surprising that adrenal cortical tumours should produce a wide range of endocrine disturbances and that analysis of the syndromes produced should still be far form complete.

However the main syndromes originally outlined by Glynn are now fairly well understood in terms of the properties of androgenic, oestrogenic and other substances known to be elaborated by the cortex and its tumours. These syndromes varying with the particular hormones secreted and with the age and sex of the patient, can be conveniently grouped thus.

(a) Tumours with no recognizable hormonal results

Examples and references are given by Kepler and Keating and by Cahill et al. Some of these growths have been highly malignant anaplastic ones but others have shown well differentiated tissues

(b) Tumours with changes due to excess af androgens

These form by far the largest group which is divisible into four sub groups according to age and sex

- (i) In female infants or children the usual results are precoeious growth and sexual development of male type with enlarged chitoris and labia and sometimes if the tumour occurs in foetal life a tressa or other malformations of the vagina. The child may thus have pseudo hermaphrodite characters and there may have been doubt as to its true sex. Adiposity may also occur. Reilly et al. reviewed 40 cases in pre adolescent girls.
- (ii) In female adults there occur voice changes hairiness of male distribution coarsening of skin acne amenorthoea adiposity the development of masculine contours and atrophy of breasts and internal genitalia
- (iii) In male children premature sexual skeletal and muscular development are observed
- (iv) In male adults as might be expected, endocrine results are often not apparent

(c) Tumours with changes due to excess af aestragens

The most striking instances are in adult males the symptoms include impotence attophy of the genitalia and mamming enlargement and secretion (Mathias Busch Burtows et al. Simpson and Joll) Oestrogen secreting tumours in adult females probably produce no special endocrine result but occurring in young children they may cause premature feminine puberty and menstruation as in Bulloch and Sequiera s case.

CHAPTER 40

TUMOURS OF THE PARATHYROID GLANDS

INTRODUCTION

When in 1891 von Recklinghausen gave his classical description of generalized fibrocystic disease of bone, the parathyroid origin of this disease was unsuspected The story of the discovery of this relationship, foreshadowed in 1904 by Askanazy's observation of a case of associated parathyroid tumour and von Recklinghausen's disease, and culminating in Mandl's successful treatment of such a case by para thyroidectomy in 1926, is well told by Drennan, Barr and Bulger, Hunter and Turnbull, Elmshie et al., Castleman and Mailory and Alexander et al., to whom the reader is referred for fuller details and examples. Before 1926, the relationship of parathyroid dysfunction and osteits fibrosa had still been debatable. Many workers had observed enlargement of the parathyroids as a secondary result of various skeletal disease, and as late as 1923, Dawson and Struthers, in their excellent account of a typical case of associated generalized osteits fibrosa and parathyroid tumour, concluded that the latter was a sequel of the former. However, the therapeutic effect of parathyroidectomy made it clear that generalized fibro cystic disease of bone was the result of hyperparathyroidssin.

Most parathyroid tumours have been classified as benign adenomas and relatively few of them as carcinomas, but, although this subdivision is useful and justifiable, there is no sharp separation of the two groups. Castleman and Mailory also sharply distinguished between cases showing generalized hyperplasia affecting all parathyroid bodies simultaneously and true neoplasms arising focally in one, or occasionally two, glands and growing progressively. However, while hyperparathyroidsm sometimes results from non neoplastic hyperplasia or hyperfunction, in most cases it is due to true tumour formation. Thus Castleman and Mallory, in their analysis of 160 previously recorded cases of hyperparathyroidsm and 25 cases of their own, found that tumours outnumbered cases of simple hyperplasia sevenfold. We are concerned here with the true tumours only but it must be admitted I think, that multiple tumour formation may sometimes be difficult to distinguish from hyperplasia.

My own experience of parathyroid tumours is limited to the following two cases, one with and the other without signs of hyperparathyroidism

Case I (Dr. J. Le. M. Kneehone's case) —History—A man 67 vears of age with advanced generalized fibrocystic disease of bone and with hypertalicienta and hypophosphatacima was operated on and a left sided parathyroid timour which extended down into the imbalastinum was removed. This weighed 60 grammes and consisted of uniform greysh brown firm tissue. A palpable timour 2 centimetres in diameter in the right side of the neck was not removed. After the operation the blood-calcium and phosphate values became normal and treatment was directed to mechanical straightening of the deformed fembrar. Histology—The tumour is a typical parathyroid adenoma consisting manly of clear principal cells arranged in cords and folded masses with small spaces and pseudo-acinium structures in places (Figs. 314 and 315).

and Heiman observed adrenal cortical tumours in rats. Berner (cited by Holmes) is said to have seen virilism in a hen with an adrenal tumour

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cerebello-pontine angle adherent to the dura above the foramen magnum and microscopically a typical menigiona and (c) multiple cortical adenomas of both adrenal glands. (The multiplicity of tumours in this case is noteworthy?)

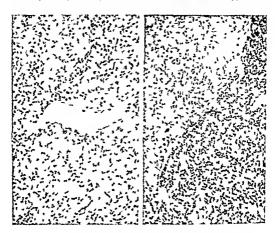


Fig. 316 -Case II Parathyroid adenoma showing distinct cell types (> 120)

INCIDENCE AND CAUSATION

(1) Age

Castleman and Mallory found the following age distribution of 154 cases of functioning adenoma

| Decades | - | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Total |
|-----------------|---|---|----|----|----|----|----|----|---|---|-------|
| Number of cases | ~ | 0 | 10 | 25 | 27 | 37 | 38 | 11 | 5 | 1 | 154 |

(2) Multiplicity

The tumours are usually single Hunter and Turnbull's review comprised 24 cases with solitary tumours and 3 cases with two tumours each

(3) Sex

In all recorded series females outnumber males, usually in the ratio of about 2 to 1 \ e g 108 women to 45 men in Castleman and Mallory's analysis, 10 to 4 in Alexander's cases

Case II —History—An obuse woman of 55 years who had had irregular metrorrhagia for 12 years underwent hysterectomy for multiple large uterine myomis and became

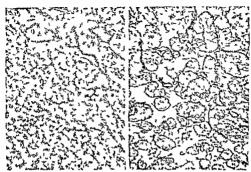
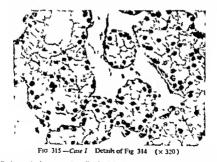


Fig. 314—Case 1 Tarathyroid adenoma clear-celled trabecular and pseudo acinar structure (x 64)

comatose and died the day following the operation. Necropsy disclosed (a) a yellowish oyold tumour 2.5 × 1.5 centimeters in the position of one of the inferior parathyroids microscopically a parathyroid adenoma composed mainly of large solid liver like oxyphil.



cells but with also areas of small cuboidal cells in actions like clusters and of vacuolated clear cells (Fig. 316)—(b) a well-defined tumour 4 centimetres in diameter in the right

described by Gentile et al, excision of the primary tumour resulted in the return of the blood chemistry to normal, the later development of a metastatic deposit in a lymph gland was accompanied by return of the chemical changes of hyper parathyroidism, which again disappeared after removal of the metastasis, and the patient remained free of further recurrence 4 years from the time of the original operation. This case was also notable in showing microscopic invasion of small verns by the growth. The cases of Alexander et al, were diagnosed as "carcinomas" because of their cytology and capsular invasion, but they produced no metastases and did not recur after removal.

THE RESULTS OF HYPERPARATHYROIDISM

Details of the now well known alterations of bone structure and blood chemistry brought about by hyperfunctioning parathyroid tumours will be found in the papers already cited, and need be summarized only briefly here

(1) The bones

The classical features of von Recklinghausen's disease are beautifully depicted in the papers of Dawson and Struthers and of Hunter and Turnbull. The principal changes are decalcification, fibrous replacement, eyst formation, osteoclastomas, and fractures and deformities. The "osteoclastomas", consisting of giant celled tissue closely resembling that of the giant cell myelomas, occur in more than 50 per cent of cases, since they disappear after removal of the offending parathyroid tumour, they are not genuine neoplasms. As Dawson and Struthers pointed out, the giant celled tissue of fibrocystic disease is a reactionary tissue related to bone resorption, and it later undergoes fibrosis and cyst formation. It is important for clinicians to know that the bone changes in hyper parathyroidism can be mistaken radiographically for Paget's disease (Couch and Robertson) and also that gicat enlargement of the jaw may simulate leontiasis (Cohen and Kelliv)

(2) The blood chemistry

The changes include risc of serum calcium and of phosphatase and fall of serum-phosphates. These revert to normal levels following removal of the offending parathyroid tumours.

(3) Urine changes

Urinary excretion of calcium and phosphates is increased. Precipitation of these leads to intra tubular calcification of the kidney and to stone formation in the pelvis (Albright et al). Renal lithiasis occurs in more than half the cases with hyperfunctioning tumours, and is sometimes the cause of the first symptoms. In some cases, nephrectomy or other surgical treatment for calculi has been carried out years before recognition of their cause, as in Cohen and Kelly's case.

(4) Metastatic calcification

This may take place in many organs besides the kidneys e.g. in the gastric mucosa and alveolar walls of the lungs in Barr and Bulger's third case and in almost every tissue of the body in the case of Dawson and Struthers

(4) Causation

Nothing is known of this. There is no evidence that simple hyperplasta of the parathyroids, whether primary or secondary to disturbances of calcium metabolism in various renal or skeletal diseases, predisposes to tumour formation. Hadfield and Rogers saw a parathyroid tumour of 64 grammes unaccompanied by hyperparathyroidism in a patient with accomegaly, and they found 6 previous reports of parathyroid adenoma or enlargement accompanying pituitary disease. Perlman also refers to the evidence suggesting a pituitary parathyroid relationship in calcium metabolism, and describes a dog in which he found pituitary adenoma adenomatous hyperplasta of the parathyroids, skeletal decalcification and chroma nephritis. I have found no other records of parathyroid tumours in animals.

STRUCTURE AND GROWTH

Parathyroid tumours are well circumscribed and many of them encapsulated its its such that the size is uniform in texture and usually brown or greyish in colour. The size attained varies, tumours of between 100 and 200 grammes have been recorded

Most of the tumours have a microscopical structure closely like that of normal parathyroid tissue consisting of trabeculae of characteristic clear cells or less often of oxyphil cells or of both. Study of the tumours confirms the opinion of most histologists that there is no essential difference between these two varieties of cells but that they are the same cells seen in different phases of activity, all combinations and transitions of the two varieties are seen in the tumours. Tumours consisting mainly or wholly of clear cells show a close resemblance microscopically to clear celled renal carcinoma especially when the presence of cystic spaces and convolution of the trabeculae give the growth a pseudo glandular pattern (see Figs. 314. 315). The structure is usually well differentiated and uniform through out only a minority of tumours showing irregularities of cellular structure and arrangement. Alexander et al. depict cellular and nuclear pleomorphism giant tumour cells mitotic figures and invasion of the tumour capsule.

MALIGNANT PARATHYROID TUMOURS

In a small minority of cases invasive properties or very rarely metastases denote some degree of malignancy. Guy Gentile et al. and Alexander et al. have reviewed the records of such cases. In some of these the details given are scanty and doubt remains regarding the identity of the tumours. Reports of malignant tumours of this region supposed to be of parathyroid origin but without evidence of hyperparathyroidism must be examined very entically, and it must be remembered particularly that a parathyroid origin has been attributed erroneously to some thyroid tumours (q v). However, in some reported cases the signs of hyperparathyroidism have been present or the structure has been characteristic. Malignancy of such cases has been restricted to local invasion of slight or moderate extent or local lymph nodal metastases. I know of no fully substantiated mistances of metastasis of parathyroid tumours by the blood stream. In Guy s case local recurrences invaded the skim. In the case

CHAPTER 41

INTRODUCTION TO MESENCHYMAL TUMOURS, FIBROBLASTIC TUMOURS AND MYXOMAS

INTRODUCTORY REMARKS ON THE MESENCHYMAL TISSUES AND THEIR TUMOURS

(1) Intermutability of mesenchymal tissues

IN THE past, students of normal histology have been too apt to assume that the different kinds of tissues and cells in the adult are permanently determined invariable structures, each a distinct immutable species capable of producing by proliferation cells of its own kind only. A study of pathological histology, ie of what the various cells can be and do in all manner of abnormal environments, soon corrects this error and shows that great transformations of cellular structure—metaplasis—are possible in most tissues. The cells have much wider potencies for differentiation than are ever displayed in health, abnormal conditions of

growth are needed to reveal their dormant potencies or plasticity

In no other group of tissues are metaplasias as frequent or as important for the pathologist as in the derivatives of the mesenchyme-fibrous, mucoid, adipose synovial, meningeal, cartilaginous, osseous haemopoietic vascular and reticulo endothelial tissues. As a striking instance of the protean potencies of reparative mesenchymal tissue may be mentioned the metaplastic formation of bone and bone marrow in scars or old inflammatory foci or in the walls of arteries Not only is the bone formed in situ, but so also are all the elements of the marrow -haemopoietic cells, megakaryocytes reticular elements and fat cells, cartilage also is often present along with the bone. None of these can be immigrants, they must all arise by divergent differentiation from the local fibroblastic and vasoformative elements of the reparative tissue Conversely bone is reconvertible 'osteitis fibrosa', Paget's disease and many other decal into connective tissue cifying and fibrous replacement lesions exemplify the fibrous metaplasia of Clearly then, the fibroblast lipoblast, osteoblast angioblast etc are not as has often been assumed sharply separate species for under patho logical circumstances, proliferating cells of these kinds may redifferentiate into cells of other kinds Proliferating mesenchymal tissue, typified by reparative granulation tissue with its fibroblasts and blood vessels, can produce all or nearly all that embryonic mesenchyme can produce. In brief, regeneration is resumed embryonic growth and metaplasias are the evidence of resumed embryonic plasticity The multiplying cells of a regenerating mesenchymal tissue "undergo a true rejuvenescence, and approach once more an embryonic condition

The cells become less differentiated de facto as well as in appearance This can only mean that some of the earlier potencies are reacquired '(Nicholson 1923)

Finally it is to be noted that not all parathyroid tumours produce hyperpara thyroidism, occasionally chineal examination or necropsy reveals a tumour which has occasioned no demonstrable hormonal results (Hadfield and Rogers and my Case II)

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Mandl F (1926) Arch klin Chir 143 1 Purlman R M (1944) Arch Path 38 20 Appreciation of the variability of the mesenchymal tissues will save the pathologist from accepting over-rigid conceptions of classification, from inventing artificial sub divisions within the main tumour types and from participating in pointless discussions over the histogenesis of tumours exhibiting aberrant differentiation

(3) "Benign' and 'malignant", relative terms

The main thesis of Chapter 3, that "innocence' and "malignancy" are not distinct properties of tumours but are merely terms of prognostic convenience, is particularly pertinent to mesenchymal tumours. Between fibromas and fibro sarcomas, lipomas and liposarcomas, chondromas and chondrosarcomas lymph omas and lymphosarcomas, no sharp lines of demarcation can be drawn Each tumout must be judged on its own ments-on its rate of growth, its cellular structure, and its powers of infiltration or metastasis. Many a 'chondroma', adjudged benign from its microscopic structure and slow rate of growth, has yet recurred or metastasized. On the other hand, many a cellular fibroma, the microscopic structure of which has justifiably caused anxiety, has yet been well circumscribed and has been cured by simple enucleation benign" giant cell tumours of bone have metastasized and proved fatal While there are, of course, a great many mesenchymal tumours the malignancy of which is plain from their microscopic structure, there are also many others for the prognosis of which great histo pathological experience is necessary-and even then mistakes will be made. In the following chapters benign and malignant tumours of each cell type are considered together-fibroma and fibrosarcoma chondroma and chondrosateoma, and so on

(4) The meaning of 'sarcoma"

A sarcoma is a malignant tumour arising from any non epithelial mesodermal tissue—fibrous mucoid, fatty, osseous, cartilaginous, synoval, lymphoid, haeno poetic, vascular, muscular or meninge il. The simplest nomenclature specifies each form of sarcoma by an appropriate prefix fibro, myxo, lipo, osteo etc. It has not been customary to think of the leukaemias, Hodgkin's disease and plasma cell tumours as "sarcomas, or to speak of malignant meningeal or synovial tumours as meningiosarcoma" or "synoviosarcoma", but it is quite justifiable to do so, for these are all malignant non epithelial mesenchymal neoplasms. Malignant tumours of serosal and vascular endothelium if such indeed occur, would also be embraced by the definition. The inclusion of all these diverse forms of growth under the one generic name 's sarcoma' is warranted not only by the common mesenchymal origin of their parent tissues, but also by their general similarity of behaviour. The definition properly excludes two special forms of malignant non epithelial tumour, gluoma and chordoma both of non mesenchymal origin.

Every kind of tumour is recognized histologically by its cellular differentiation. An epithelial tumour can only be recognized as such if its cells show some degree of epithelial aggregation, it as often happens a carcinoma is so anaplastic that its cells have lost all polarity and arrangement, then the microscopist cannot affirm its epithelial nature. So also, the microscopist alone can affirm the sarco matous nature of a tumour only when it displays a recognizable degree of

Histologists describe the presence in the connective tissues of the adult body of undifferentiated mesenchymal cells. These presimably have the potencies of embryonic mesenchymal cells and may be supposed capable of differentiating into any of the adult tissues derived from mesenchymal. It is quite probable that these cells may be the source of some of the mesenchymal turnours. But it would be splitting hairs to debate whether or not these cells or the differentiated cells of the tissues are the usual origin of turnours for most kinds of adult cells of mesenchymal origin can multiply and when they do so they often display their reacquisition of embryonic potencies by redifferentiating in aberrant directions. The young multiplying progeny of formerly differentiated cells probably possess plumpotence equivalent to that of undifferentiated mesenchymal cells which have never matured.

(2) The kinship of the various mesenchymal tumours

The plasticity or capacity for diverse differentiation plainly seen in simple regenerative proliferations of the mesenchymal tissues is amply evident also in their tumours and has led to many needless disputes over histogenesis and classification and to complicated and redundant terminology. Names like fibro angio myxoma or haemangio elasto myxoma or chondro myxo haem angio endothelio sarcoma (names which have actually been used) while they may be tolerable as shorthand descriptions are all too apt to be invested with histogenetic implications and so to impede clear thought. The very use of such names shows plainly the plasticity of the proliferating tissues a plasticity which makes a rigid classification of mesenchymal tumours impracticable. Fibromas chondrify or ossify osteogenic sarcomas contain cartilaginous or fibrous areas . fibromas contam myxomatous areas and vice versa lipomas are often partly or predominantly fibromatous the fibromatous component of mammary fibro adenomas becomes cartilaginous or bony predominantly vasoformative (angio matous) areas are found in tumours of other kinds all eradations and combinations are seen between the several named variants of lymphoid tumourslymphatic leukaemia lymphosarcoma Hodekin's disease and reticulosarcoma. and endless confusion has resulted from attempts to segregate a group of endo thehomas from other mesenehymal growths. Of great interest is a report by Gilmour of a recurrent tumour in an adult which consisted of mucinous tissue like embryonic mesenchyme with also lipoblasts and haemopoietic cells, and for which therefore the suggested name mesenchymoma ' is appropriate

Of course just as it is necessary and useful to distinguish by appropriate names the various differentiated normal tissues derived from mesenchyme so also it is necessary and useful to distinguish by corresponding names the various tumours showing predominant differentiation of this or that type. It is also true that the fund of differentiation exhibited by a tumour is in most cases wholly or mainly that of the tissue from which it has sprung e.g. that osteogenic tumours usually spring from bone cartilaginous tumours from cartilage fibroblastic tumours from connective tissue and so on. The cell types of the several differentiated kinds of mesenchymal tissue naturally tend to be perpetuated in their tumours. But it is a mistake to be misled by terminology into assuming that the species either of the normal tissues or of their neoplasms are unrelated and immutable.

that cell will cease to be "endothelial". So also synovial "endothelium" consists merely of mesenchymal eells which have come to line a synovial cavity sharp distinction can be made between these cells and the subjacent fibroblasts of the synovial membrane Synovial "endothelium" and synovial fluid can develop from non synovial connective tissue when mechanical conditions are appropriate, as in false joints and bursae. The special properties of endothelial cells of all kinds are, in fact, properties acquired by mesenchymal cells placed in certain positions with respect to special body fluids or other environmental factors

(11) Do characteristic tumours arise from endothelium? Tumours do, of course, arise from and tend to reproduce the specific structures of, vascular, synovial or meningeal tissues But these aircady have their appropriate names and nothing is gained by embracing them under the further common label 'endo thelioma', an angioma, a synovioma and a meningioma have no more in common than other tumours of mesenchymal origin. To force them together under a common name merely because they all represent tissues which have flat celled surfaces is artificial and an affront to histogenetic principles necessary to add here that most so called 'angiomas" are not even tumours, but malformations, so that their artificial alliance with true tumours like menin giomas is particularly confusing

If it be argued that the name "endothelioma" (or "mesothelioma") is still useful to designate a distinctive group of malignant tumours with vasoformative, reticulo endothelial or coelom formative characters, I reply (a) that for the very rare malignant angiomas the name "angiosarcoma" is preferable, as being uniform with the names of other specific kinds of sarcoma and as being less cumbersome than "haemangio endothehoma", (b) that for the rare spindle celled or pleomorphic celled primary tumours of lymphoid tissue "reticulo sarcoma 'is the appropriate specific name, (c) that I have not seen an acceptable report of a primary coelomic endothelioma, and that the only tumour which I myself ever ventured to diagnose as such, a tumour in a hydrocele, turned out to be a metastasis from an undetected bronehial carcinoma (Willis, 1938), and (d) that the great majority of reports of supposed 'endotheliomas" whether of lymph tlands, serous cavities or bones are either wholly inadequale or carry clear internal evidence that the tumours were secondary to undiscovered primar) growths elsewhere (see Chapter 10)

Further, there are no histogenetic grounds for supposing that a sarcoma arising from the layer of cells lining a vascular or coelomic space would be any different from a sarcoma arising from the immediately extravascular or subserous cells As we have seen the surface cells are what they are by virtue of their post tions If in a tumour they cease to hold surface positions they will cease to be "endothelial 'cells Confronted then by a cellular vascular sarcoma, how shall we decide whether on the one hand it arose exclusively from preformed vascular endothelium and that its vessels display its vasoformative properties or on the other hand from indifferent fibroblastic or other mesenchymal tissue and that its vessels represent rerely the mevitable blood supply of a growing cellular tissue? The problem is the same as that of the origin and potencies of the vascular and extravascular cells in reparative tissue, and the solution is the same namely, that all these young mesenchymal cells are plastic and interconvertible, and disputation over their endothelial' or "non endothelial' nature is pointless

differentiation towards one or another of the non epithelial mesodermal tissues 10 if it is recognizable as a fibrosarcoma an osteosarcoma a leiomyosarcoma etc. A completely anaplastic sarcoma is indistinguishable by microscopic study alone from any other completely anaplastic growths. These considerations though self evident are constantly being ignored in medical and pathological Neoplasms are dubbed sarcomas (round celled . mixed celled or giant celled) merely because parts of them celled often only small biopsy fragments, have been found diffusely cellular Some writers go even further in their preconceptions of sarcomatous structure and seeme enthelial clumping amidst diffuse tumour tissue call tumours alveolar careno sarcoma or sarcoma carcinomatoides of confusion have already been discussed in Chapter 8 (and see Willis 1932) Here I reneat my conviction that excluding tumours sufficiently differentiated for positive histological identification, there is no type of structure alleged to be characteristic of any form of sarcoma (or endothelioma') which may not he perfectly imitated by areas of atypical carcinoma

This warning against the all too prevalent mistake of calling tumours ' sarco just because they are anaplastic and diffusely cellular does not of course amply denial of the existence of anaplastic cellular sarcomas. But the recognition of such tumours as sarcomas depends upon evidence other than the microscopic namely on the knowledge that the primary growth arose in some non-epithelial organ such as a lymph cland a bone or a muscle and this knowledge is often not certain unless complete necropsy has shown that the presumed primary growth was indeed arimary and not a metastasis from some unsuspected tumour elsewhere Histological diagnosis must not be allowed to run ahead of the available evidence and when the evidence is still inconclusive the wise pathologist will be content to

undifferentiated cellular malignant neoplasm of uncertain origin

(5) Endothelioma

This is the place to record once and for all my opinion of this much abused name. Two questions must be answered-(i) What is endothelium? and (ii)

Do any specifically characteristic tumours arise from it?

(i) What is endothelium? Most would agree that this name is usefully applied to the flat layers of cells liming vascular and serous cavities, to which some would add the layers of cells having menungeal and synovial cavities. Now both embry ology and pathology show plainly that these flat layers of cells are endothelial not by virtue of any specific properties of the cells but by virtue of their positions Studies of the proliferation and fate of fibroblasts and vasoformative cells in reparative tissue show that vascular channels in this tissue appear and disappear repeatedly in accordance with purely mechanical factors. This plasticity of all the elements in young mesenchymal tissue should cause no surprise to the patholo gist and surgeon both of whom know well that the highly vascular granulation tissue of today rich in endothehal channels will in a few weeks be an avascular scar devoid of endothelium and containing only fibrocytes The young multiplying cells in the reparative tissue are ready to become either endothelial cells or fibro cytes (yes or osteocytes or chondrocytes or fat cells or hacmoporetic cells) as may be determined by local conditions. An endothelial cell is merely one which has come to line a vascular channel and when that channel disappears

Between cellular anaplastic highly malignant growths of this kind and slowly growing, densely fibrous, benign growths structurally resembling normal fibrous ussue, there is a complete series of tumours of intermediate structure and behaviour

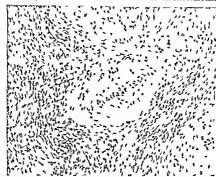


Fig. 317—An area of early chondrification in a partly cartilaginous subcutaneous fibroma 3 centimetres in diameter from a woman aged 27 (× 120)

Moreover, primarily fibrifying tumours cannot be sharply separated from other mesenchymal growths, for some of them show metaplastic mucinous change, chondrification or ossification (Fig. 317), or admixture with adipose cells. It is merely a matter of personal preference whether to apply to these tumours such names as 'ehondro fibroma' and "myxo fibrosarcoma" or to call them "chondrifying fibroma" and "fibrosarcoma with mucinous change".

I do not intend to repeat the well known descriptions of the structure of firms and fibrosarcomas—their varying degrees of cellularity and of collagen content, the latter determining their texture and their hardness or softness. All gradations and combinations between dense tendon like fibrous tissue and undifferentiated pleomorphic celled sarcoma are encountered. The latter shows great cellular variety, often including many giant and multinucleited tumour cells, the fibroblastic nature of these, and also of poorly collagenous spindle celled fibrosarcomas is often uncertain. For it is difficult to distinguish included collagen fibros from fibres formed by the tumour cells.

(2) General behaviour

While highly differentiated, densely fibrous tumours usually behave as benign fibromas there are exceptions to this rule as in the following two examples

Case I (reported in detail in 1938)—History—A man aged 49 had noticed a swelling of his tibia for a year. Skingrams showed an expanding central radio translucent lesion thought to be either osterits fibrosa or a beingn tumour. Excision of the middle third of the tibia with insertion of a bone graft was performed. The lesion showed dense

Briefly then, my position is that for well differentiated growths of those mesenchymal tissues which happen to possess surfaces we already have adequate distinctive names and that for poorly differentiated surromatous growths of these tissues the name endothelioma is still unnecessity and in view of what we know of the plasticity of multiplying mesenchymal cells, inappropriate

(6) The ubiquity of mesenchymal tissues and regional peculiarities of their tumours

Mesenchymal tissues are ubiquitous so that no part of the body is exempt from mesenchymal tumours. This widespread distribution of tumours of any given type makes a general analysis of their properties not only difficult but also of doubtful value for differences of site are accompanied by differences of behaviour. Thus fibromas of nerve sheaths fibromas of bones and fibromas of the abdominal wall though all consisting of broadly similar fibroblastic tissue—show many differences of age and sex incidence structure and behaviour. Strictly speaking then the only satisfactory way of discussing the characters of tumours of a given cell type is to do so piecemeal region by region. This however would entail a great deal of repetition regarding those general features of structure and behaviour which are common to the whole class. In the following chapters I have attempted to strike a compromise between a broad survey of each class and particular accounts of those regional subclasses with peculiar features. In doing this I have dehiberately omitted or curtailed descriptions of those characters of the various tumours which are well known and adequately presented in most text books and have preferred to draw attention to fess familiar features and veryonous

(7) Frequency and causation of mesenchymal tumours

Considering the abundance and ubiquity of mesenchymal tussues in the body, and their ready proliferative response to injury mesenchymal tumours are surprisingly infrequent. This fact alone is significant as regards the supposed traumatic and irritational causation of tumours although reparative and chronic inflammatory changes are everyday occurrences mesenchymal neoplasia is rare Experimental results confirm this fibroblastic and other sarcomas though readily evoked by specific carcinogenic agents are rarely if ever produced by non specific injuries (see Chapter 4). The mesenchymal tumours produced experimentally by carcinogenic agents resemble in structure and behaviour those occurring spontaneously in animals and man. It therefore seems reasonable to assume that the spontaneous growths are likely to be due to similar specific agents and to search for these in the histories and environments of the patients. At least one kind of mesenchymal tumour in man the osteosarcoma of workers in radio active materials is already known to be caused by an external agent.

another leukaemir in benzol workers is strongly suspected. and further instances will no doubt be brought to light by future research.

PREDOMINANTLY COLLAGENOUS TUMOURS FIBROMA AND FIBROSARCOMA

(1) General structure

Mesenchymal tumours the cells of which recognizably differentiate as collagen forming fibroblasts are fibromas or fibrosarcomas according to their behaviour

as some workers have done, that all or most fibroblastic tumours are neurogenic, there are many fibromas devoid of evidence of a relationship to nerves

(4) Dermal fibromas

(a) Scierosing angiomas

The skin is, of course, an important site of neurofibromas. But in addition to these, there also occur in the dermis small well defined but non encapsulated yellowish tumours consisting of spindle shaped, irregular or multangular fibro blasts along with more or less abundant collagen and thick walled narrow blood vessels, well depicted by Harvey et al in their Figures 16-19 The collagen fibres are often densely aggregated into well defined sometimes hyalinized bands, continuous at the tumour margins with the fibrous bands of the dermis These growths have been variously designated by derinatologists and pathologists as dermatofibroma", "xanthofibroma", "selerosing angioma", "fibrosarcoma" and 'spindle cell sarcoma" (Stecker and Robinson) They are indolent, quite benign growths, rarely attaining a diameter of more than 1 or 2 centimetres in as many years, and not suffering ulceration save accidentally. Most of those which I have studied have been from the foot or leg but I have seen them also from the hand forearm, thigh and neck. Their precise histogenesis is uncertain. The absence of encapsulation and the occasional inclusion of dermal nerves in their spreading margins do not justify the assumption that they are neuro fibromas, which in other respects they do not resemble. Their plentiful content of small vessels or of structures like obliterated vessels suggests the probability that they are scienosing angiomas. The cause of their vellow colour deserves further investigation, it is not due to foam cell accumulations, Harvey et al. demonstrated intra cellular basemosiderin in one of their specimens

(b) Keloids

Keloids form a distinct class of growths of the dermis These densely fibrous, persistently recurrent hyperplastic scars are adequately described in most surgical works. It is doubtful whether they are true neoplasms, the local or general predisposition of the skin of those affected, the special liability of dark skinned races to keloid formation and the general characters of the lesions, all suggest rather some non neoplastic disturbance of reparative growth

(5) Fibroma or ' desmoid tumour" of the abdominal wall

This rare growth, 66 specimens of which were reviewed by Stewart and Mouat (1924) and 77 by Pearman and Mayo (1942) is a very distinctive one. In more than 80 per cent of the cases the patients have been parous women and in most of the remainder of the cases the growths have arisen at the sites of operation scars or other injuries. The tumours develop usually during the third or fourth decades of life. They arise from the muscular aponeuroses of the abdominal wall usually below the level of the umblicus and only rarely in the midline They are non encapsulated, and infiltrate the neighbouring muscles which become sincluded and atrophied in the growth. They may attain a great size 17

fibrous tissue with cysts and was diagnosed microscopically as ostetis fibroa. The graft failed a sinus persisted and amputation through the upper third of the leg was performed? From on this later. The patient then remained well for a year when swelling of the amputation stump was noticed. Stiagrams showed a large soft tissue mass and irregular erosion of the ends of the tibia and fibrila. Re amputation through the lower third of the femir was performed. Examination showed a large mass of hard fibrous tissue enveloping the bone ends and infiltrating the muscles and skin. microscopically a densely fibrous poorly cellular tissue like a hard fibroma.

Case II - History - In March 1925 a parous woman aged 65 noticed a small lump in her right calf. A year later when it had attained the size of a tennis ball it was excised at was well defined situated between the calf muscles and unattached to skin or bone Microsconically it showed densely fibrous poorly cellular fibrous tissue and was diagnosed hard fibroma The patient remained well for 18 months then late in 1927 recurrence of the growth was noticed. In May 1928, she first noticed a hard mass in her left lower abdominal wall this slowly enlarged. In November 1929 when she was admitted to hospital the tumour in the calf had grown to a large size measuring 15 centimetres in length with commencing ulceration the abdominal wall contained a large hard nodular mass unattached to the skin. In January the calf tumour underwent rapid ulceration and death occurred in February 1930 at the age of 70 Necrops)-Extensive ulcerated soft growth of right calf replacing muscles but unattached to bone no metastases Lobulated hard fibrous mase 10 centimetres in diameter superficial to but adherent to the aponeurosis and muscles of the left lower abdominal wall Histology-Calf tumour consisted partly of well differentiated fibroma like tissue partly of undifferentiated sarcoma with many large HTEGUIAT and multinucleated cells. Abdominal tumour was a densely fibrous partly hyaline poorly cellular fibroma

These cases show that seemingly benign fibromatous structure is compatible with malignant growth properties. In most cases however the structure of malignant fibroblastic tumours accords with their behaviour some degree of cellular anaplasia is present and mitotic figures are easily found. The main risk of such tumours is metastasis by the blood stream to the lungs and elsewhere metastases in lymph glands, as in cases reported by Warren and Meyer are relatively infrequent.

The behaviour of fibroblastic tumours differs with their sites of origin justifying separate consideration of the several regional groups of growths now to be described.

(3) Fibroblastic tumours of nerve sheaths

Chapter 54 gives an account of nerve sheath tumours and of the controversy regarding their histogenesis. This need not concern us here. Suffice it that there do occur tumours of nerves—neurofibromas and neurofibrosarcomas—which consist wholly or predominantly of collagen forming fibroblastic tissue and that probably many fibroblastic tumours not demonstrably related to nerves are nevertheless of nerve sheath origin (Stewart and Copeland). The ground for this second assumption is that the more thoroughly fibromas and fibrosarcomas of doubtful origin are examined the more often evidence of their relation to nerves is detected. Such evidence comprises the entry of recognizable nerves into the tumour, the presence of medullated or non-medullated nerve fibres within the tumour, or extensions of tumour tissue along nerves marginal to it whorling and myvoid change are also suggestive but not conclusive. Deliberate search for these features in fibroblastic growths will sometimes establish beyond reason able doubt their neurofibromatous nature. However, it is a mistake to assume

polypi and "juvenile nasopharyngeal fibromas" continue to figure in many text books as tumours. The tendency of these lesions to recur, to spread over

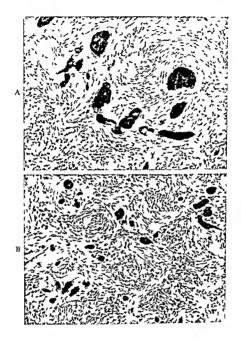


Fig. 318—Case III Fibroma of the maxilla with calcified foci. A = upper part of tumour where the calcified foci are clearly derived from included residues of bone. B = central part where whorted structure and calcified spherules simulate meningioma. (Cp. Fig. 320) (x. 120).

a wide field of diseased mucosa and to lead to infective complications in adjacent cavities bones and other tissues, has given them a false clinical reputation of neoplastic qualities. The nature of the rare "malignant granuloma' of the nasal cavity is also open to doubt, the cytology and destructive invasiveness of

kilograms in one case and recurrence may follow incomplete removal. In spite of these features, the tumours are not malignant, neither metastasis nor micro scopic evidence of sarcomatous change has been recorded. Large tumours undergo mucoid or cystic degeneration and may rapidly increase in size from minimization of fluid this must not be mistaken clinically for malignant change. While it may well be that the coexistence of a fibroma of the abdominal wall and a fibrosarcoma of the calf in my Case II above was fortuitous, the possible existence of a general predisposition to fibroblastic neoplasia must also be admitted

(6) Fibroblastic tumours of bones

Cappell described an endosteal fibroma of the fibula from a man of 32 years and Jaffe and Lichtenstein described 10 similar growths in the shafts of long bones in patients from 6 to 21 years old of both seves. All of these tumours proved to be benign but that some central fibroblastic tumours of bones are malignant is shown by my Case I above. According to Stewart and Copeland, parosteal fibrobaracomas are often of neural origin and associated with stigmata of neurofibromatosis. Peers described an endosteal neurogenic sareoma of the ulna. Steiner saw a remarkable case of multiple diffuse fibrosarcomas of many bones.

Fibromas of the jaws, distending the bones or filling the maxillary antrum, have been well described by Boemke Giessen and the following example deserves record

Case III — A man aged 26 years had noticed a gradually increasing swelling of the left side of his face for 7 years. This had been variously disanceded as dental cyst osteoma and leontiasis. Skiagrams showed opocity and distension of the antrum with erosion of its inferior and lateral walls. A biopty specimen showed fibromatous tissue of beingin appearance and operative removal was therefore undertaken. The large tumour was found to spring from the floor of the antrum which it filled and distended. The upper surface of the growth stripped away smoothly from th, orbital wall but parts of the palate and nasal wall had to be removed in order to effect its complete removal. Over 70 grammes of tumour tissue were removed. Bissiology (Fig. 318)—The was a well differentiated hibrous tumour of moderate cellularity but with few or no mitotic figures partly clothed on its upper surface by a bowt shell and containing scattered rounded or elongated calcified granules. These probably developed from residues of necrotic bone spicules included in the tumour continuity of the calcified masses with fragments to bone was evident in the upper portion of the growth. Progress—There was no evidence of recurrence 18 months later.

The attachments of the growth and the presence of a shell of bone on its upper surface in this case show that it arose in the maxilla and pushed the bony floor of the antium upwards as it expanded into this cavity. The scattered calcification in the tumour closely resembled that described by Boemke Giessen and that present in the nasal fibroma in dog No 4 below it is evidently a special feature of fibromas of this region.

(7) Nasal and nasopharvngeal fibroblastic tumours

While true fibroblastic tumours of the nasal and nasopharyngeal mucosa may rarely occur most of the so-called fibromas and mycomas are not neoplasms but inflammatory or illergic overgrowths. It is regretiable that nasal tumours—rarer than oedematous fibromas, with which they must not be confused Only the demonstration of mucin justifies the diagnosis of myxoma (Fig 319) Fibroblastic tumours of nerve sheath origin, especially the malignant ones, are particularly liable to partial myxomatous change Most of the few myxomatous growths which I have examined showed structural evidence of a nerve sheath origin or were from situations which suggested the likelihood of such an origin

Intercellular mucin may appear also in mesenchymal tumours of other kinds, especially cartilaginous and adipose tumours (q v) Sylven has advanced the idea that mucinous change in mesenchymal tumours is a manifestation of proteo lytic activity of the tumour cells and is related to their invasiveness, but the evidence is unconvincing

Most prominently myxomatous tumours are to be regarded as malignant, in that they are prone to recur after attempted removal and eventually to metastasize The attempt to distinguish benign myxomas and myxosarcomas is even more futile than with their collagenous counterparts

Endocardial myxomas and pseudo-myxomas

For good accounts of these, see Yater, Muller and Fawcett and Ward They are rare polypoid growths which spring from the endocardium usually of the left atrium. As Muller pointed out, diverse lesions have been placed in this group, including true endocardial tumours, tumours of the heart wall invading the chambers, and unorganized or organizing thrombi. Often, although the growths may have a myxomatous appearance to the naked eye, special stains have failed to confirm the presence of mucin (Muller), but in other tumours, as in that described by Orr, abundant mucin has been present doubt that, while oedematous organizing thrombi have sometimes been mistaken for tumours, there are genuine endocardial fibroblastic neoplasms with a tendency to mucinous change Orr's view that the tumours are "essentially endothelio matous" is, I think, unnecessary, and his comparison of them with the so called 'mixed' salivary tumours, which are simple epithelial growths, is unfortunate Most of the reported tumours have been non invasive and benign, but in Muller's first case, the tumour diagnosed as a fine-fibred fibrosarcoma had produced metastases in the lungs A small tumour of the aortic valve described by Yater as a "papilloma' consisted of a bunch of fine endocardial villi clothed by endothelium

FIBROBLASTIC AND MYXOMATOUS TUMOURS IN ANIMALS

Fibroblastic tumours are commoner m many species of animals than in man Feldman's Chapters IV and V and Chapter 6 of this book give many references to fibromas fibrosarcomas and myxomas in horse, cattle swine dogs, cats rodents, buds, reptiles and fish In their range of structure and behaviour these growths resemble the human ones, and some of them show similar evidence of origin from nerve sheaths

Not including a number of spindle celled and pleomorphic celled sarcomas which were probably fibroblastic but were too undifferentiated for certain

this lesion certainly suggest, but do not conclusively prove, that it is a malignant tumour

(8) Fibromas of the ovary

Excluding the cortical fibro papillary tumours in which both surface epithelium and fibrous stroma participate fibromas of the ovary usually arise not from the simple fibroblastic framework of the organ but from its undifferentiated mesenchyme which is its peculiar parenchyma (see Chapter 29) Granulosa cell theca cell and lutteal cell tumours are all related ovarian folliele tumours and most or all fibromas are of the same group representing the most matured

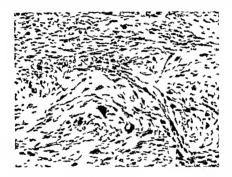


Fig. 319—Myxosarcoma From a subcutaneous mucin rich tumour 8 centimetres in diameter noticed growing for 9 months in abdominal walt of a woman of 61 years (> 170)

end product of the series just as the corpus fibrosum is the end product of the maturation of the normal follock

PREDOMINANTLY MUCINOUS TUMOURS MYXOMA AND MYXOSARCOMA

Just as for the histologist the presence of intercellular mucin is the only teature distinguishing mucoid from collagenous connective tissue, so for the pathologist this is the only feature distinguishing mytomas from fibromas. There is no such cell as a myxoblast distinct from a fibroblast. The formation of mucin in the matrix of young mesenchymal tissue, is widespread in the embryo and re appearance of this property in some fibroblastic growths is not surprising Myxomas and myxosarcomas are then merely fibromas and fibrosarcomas in which mucin his developed in the intercellular matrix. They are relatively rare

mingled with the normal structures of the affected part, which may show other developmental anomalies also, such as deformation of bones and muscles or angiomas. Doubtless, some of these congenital "lipomas" are not true tumours, but hamartomas—superfluous tumour like masses of improperly blended tissues, comparable with most "angiomas", and without powers of disproportionate progressive growth. In many other cases, however, the tumours do grow progres sively and attain large sizes, thus displaying their neoplastic qualities. The following examples from the voluminous literature will exemplify the range of situation and structure of these interesting growths.

Butlin removed a large well circumscribed encapsulated tumour from deep in the calf and interosseous space of the leg of a child aged 7 years. The tumour had been noticed since the child's first year and had grown steadily Microscopically it showed adipose and fibrous tissue in about equal amounts, it contained also many strated muscle fibres which could be traced into the growth from its capsule and which had probably been enclosed in the tumour as it grew and were not of new formation. (Cf. Cases III and IV below)

Lockwood described bilateral congenital fatty tumours of the feet, and a congenital lipoma of the palm of the hand, Powers, a congenital fatty tumour connected with the periosteum of the femur, and Bland Sutton depicted and referred to similar cases. Eve described an unusually large congenital lipoma, weighing 3½ pounds, removed from the abdominal wall of a girl of 13 years Adair and co workers described a child with Frohlich's syndrome and congenital lipomas of the hand and arm, a negro girl with large multiple tumours of the forearm arm avilla and shoulder, accompanied by deformities of the limb bones and an infant 5 months old with diffuse lipomatosis of a lower limb accompanied by two cavernous angiomas of the same limb

Baker and Adams described multiple lipomas of the choroid plexus, base of the brain and spinal canal in a hydrocephalic female infant who also had defects of the skull, xanthomas of the cyclids and malformed irises. These writers reviewed reports of similar cases, which showed other associated malformations including agenesis of the corpus callosum, absence of the kidney, hare lip and cleft palate (On lipomas of the central nervous system see also Krainer) Large masses of fat, often called 'lipomas", may overlie spina bifida or meningocele

The following personally studied case affords an interesting example of the admixture of congenital lipomatous tissue with the structures of the part

Case I—A healthy female infant 5 months old had had a swelling below the right angle of the mandible since birth with slight increase in size since. It was easily enceleated and proved to be a well defined nearly spherical slightly lobulated mass 42 centimeters in diameter 19 grammes in weight. On section it appeared to consist of firm pale adjunct insue throughout. Microscopical examination of many sections showed overywhere the same structure namely fully differentiated adjunce tissue containing also plentful glandular tissue consisting of branching ducts and relatively scanty simple acun (Figs. 321 and 322). Some compressed parotid tissue was attached to the capsule of the tumour and it was clear that the glandular elements in the tumour consisted of salivary tissue which had been incorporated within a congenital lippina.

diagnosis Rudduck and I examined the following fibroblastic tumours from animals

| No | Anımal | | Turnour | Necropsy findings |
|----|---------|--|--|--|
| 1 | Dog | - Fibroma (* neurofibroma) of skin of hock | | |
| 2 | Dog | ~ | Fibroma of vagina | |
| 3 | Dog | ~ | Fibro arcoma of skin of neck | Metastases in lymph glands lungs pleura heart liver kidneys |
| 4 | Dog | - | Librosarcoma of nasal cavity (Fig. 320) | Huge tumour 11 centimetres in man diam ter with granular calcification (cp Case III above) No met astases |
| 5 | Dog | - | Fibrosarcoma of medinstinum | Metastases in lungs heart liver peri |
| 6 | Dog | - | Fibrosarcoma of neck | No metastases |
| 7 | Dog | - | I ibrosarcoma of skin of thigh | Metastases in lymph glands |
| 8 | Dog | _ | Fibrosarcoma of skin of chest | ~ |
| 9 | Cat | _ | Fibrosarcoma of skin of foot | |
| 10 | Cat | - | Neurofibrosarcoma of foot | No metastases |
| 11 | Horse | _ | Neurofibroma of skin of buttock | |
| 12 | Horse | ~ | Fibrosarcoma of skin of fetlock | |
| 13 | Parakee | et ~ | Myxoma of subcutaneous tissue near wing base | - |



Fig. 320 -- Nasal fibroma with focal catchication from a dog. (Cp. Fig. 318) (× 120)

Notable points are that at least 8 of the 13 tumours were from the skin or subcutaneous tissues that at least 3 were of neural origin, and that fibrosarcomatous metastases in 1 Jimph glands were present in 2 case. mungled with the normal structures of the affected part, which may show other developmental anomalies also, such as deformation of bones and muscles or angiomas. Doubtless, some of these congenital "lipomas' are not true tumours, but hamartomas—superfluous tumour like masses of improperly blended tissues, comparable with most "angiomas", and without powers of disproportionate progressive growth. In many other cases, however, the tumours do grow progres sively and attain large sizes, thus displaying their neoplastic qualities. The following examples from the voluminous literature will exemplify the range of situation and structure of these interesting growths

Butlin removed a large well circumscribed encapsulated tumour from deep in the calf and interosseous space of the leg of a child aged 7 years. The tumour had been noticed since the child's first year and had grown steadily Microscopically it showed adipose and fibrous tissue in about equal amounts, it contained also many striated muscle fibres which could be traced into the growth from its capsule and which had probably been enclosed in the tumour as it grew and were not of new formation. (Cf. Cases III and IV below)

Lockwood described bilateral congenital fatty tumours of the feet, and a congenital lipoma of the palm of the hand, Powers a congenital fatty tumour connected with the periosteum of the femur and Blind Sutton depicted and referred to similar cases. Eve described an unusually large congenital lipoma weighing 3½ pounds, removed from the abdominal wall of a girl of 13 years Adair and co workers described a child with Frohlich's syndrome and congenital lipomas of the hand and arm, a negro girl with large multiple tumours of the forearm arm axilla and shoulder, accompanied by deformities of the limb bones, and an infant 5 months old with diffuse lipomatous of a lower limb, accompanied by two cavernous angiomas of the same limb

Baker and Adams described multiple lipomas of the choroid plexus, base of the brain and spinal canal in a hydrocephalic female infant who also had defects of the skull, xanthomas of the eyelids and malformed inses. These writers reviewed reports of similar cases, which showed other associated malformations including agenesis of the corpus callosum absence of the kidney, hare lip and cleft palate (On lipomas of the central nervous system, see also Krainer) Large masses of fat, often called "lipomas" may overtie spina bifida or meningocele

The following personally studied case affords an interesting example of the admixture of congenital lipomatous tissue with the structures of the part

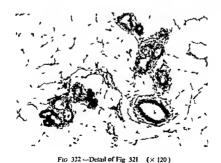
Case I—A healthy female infant 5 months old had a swelling below the right angle of the mandible since birth with slight increase in size since. It was easily enullented and proved to be a well defined nearly spherical slightly lobulated mass 42 centimetrs in diameter 19 grammes in weight. On section it appeared to consist of firm pale adipose insure throughout. Microscopical examination of many sections showed everywhere the same structure namely fully differentiated adipose insure containing also plentful glandular tissue consisting of branching ducts and relatively scarify simple acmi (Figs 321 and 322). Some compressed parotid tissue was attached to the capsule of the tumour and it was clear that the glandular elements in the tumour consisted of salivary tissue which had been incorporated within a congenital lippoma.

BENIGN LIPOMAS AND FIBRO LIPOMAS OF ADULTS

I propose to say little of the chinical characters and gross structure of these, which are sufficiently described in most text books



Fig 321 - Case I Congenital lipoma with included parotid glandular tissue (× 41)



(1) Age, sex, site and number

While no age is exempt most lipomas develop in middle aged or elderly people the mean age in 23 cases which I have seen was 25 years. The mean age in Adair's and co authors series was 41 years but these included congenital as

well as adult cases Since many patients have had their tumours for several years before undergoing operation, the mean age of actual onset must be considerably less than that usually recorded Although Adair and co authors found that 73 per cent of lipomas were in females, it is doubtful if this obtains generally, of my 23 cases, 12 were women and 11 were men. The commonest sites are the subcutaneous tissues of the limbs or trunk, and the retroperitoneal tissues and inguinal canal. Submucous lipomas of the larynx, oesophagus, stomach or intestine, and lipomas of solid viscera, are rare. Most lipomas are solitary, two or three tumours are not unusual, numerous multiple ones are rare. Adair et al described a man with 160 subcutaneous lipomas. There are good grounds for regarding the eases with many lipomas as belonging to a distinct and peculiar group (see below). Lipomas may attain luge dimensions, the largest recorded being the retroperitoneal lipoma reported by Delamater (cited and depicted by Stout) which weighed at least 179 pounds and possibly 275 pounds.

(2) Causation

(a) Congenital predisposition

The remarkable characters and variety of the congenital lipomas, described above, have led Ewing and others to postulate a "congenital tissue predisposition" for lipomas generally Support for this view is afforded by the occasional instances of an heredo familial predisposition. Thus Adair et al. described a woman 53 years old who had 16 subcutaneous lipomas, and whose two sons and a grandson also had multiple lipomas, and these writers refer to other records of familial cases. However it is very doubtful if any congenital predisposition obtains for the ordinary solitary lipomas appearing during adult life. These are probably unrelated to the congenital tumours, and they show no significant familial incidence

(b) Relation to the nervous system

Adair and co workers have advanced reasons for believing multiple lipomas to be related to disturbances of innervation. Thus, these tumours show many points of similarity to neurofibromatosis—namely, their usual appearance in adolescents or young adults, their symmetrical distribution, the presence of sensory or trophic disturbances in some cases, of skin pigmentation in some cases, of an hereditary tendency, and the occasional coexistence of lipomas and neurofibro matosis. Adair et al also thought it probable that congenital lipomas may be related to nerves or to disturbed innervation. Hueper refers to cases of acquired multiple lipomatosis issociated with injury or disease of the spinal cord or nerves. There is need of further careful structural studies of congenital and acquired multiple lipomas and their possible relation to peripheral nerves or to disease of the central nervous system.

(c) Trauma

Ewing and others have supposed trauma to play a part in the genesis of lipomas and liposarcomas, but except for the rare instances of multiple lipomas associated with spinal injuries, there is no substantial evidence for this view

BENIGN LIPOMAS AND FIBRO LIPOMAS OF ADULTS

I propose to say little of the clinical characters and gross structure of these, which are sufficiently described in most text books



Fig. 32t -Case I Congenital lipoma with included parotid glandular tissue (x 41)



Fig 322 -- Detail of Fig 321 (y 120)

(1) Age, sex, site and number

While no age is exempt, most lipomas develop in middle aged or elderly people the mean age in 23 cases which I have seen was 52 years. The mean age in Adurs and co authors series was 41 years but these included congenital as the malignant part of the growth is a fibrosarcoma, not a liposarcoma (Fig 326). The term "liposarcoma" should be applied only to tumours whose cells are malignant lipoblasts.

Further caution is needed before dubbing a tumour "liposarcoma" just because it contains fat laden cells. Many kinds of anaplastic tumours show tumour cells with fat or lipoid droplets due to degenerative changes, and of course macrophages laden with such materials are often plentiful in tumours. When dealing with a cellular tumour of uncertain nature, which might be a liposarcoma, all other possibilities must be considered, and the diagnosis must sometimes remain uncertain unless complete necropsy has proved the absence of an unsus pected primary growth of other nature clsewhere. Some cases reported as "lipo sarcoma" (e.g. Stewart's case 2) are open to doubt on these grounds



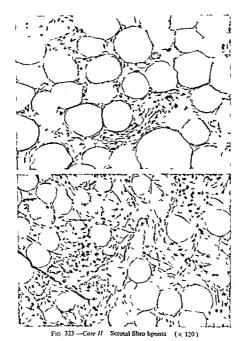
Fig. 326—From a myxosarcomatous part of a large retroperitoneal lipoma in a man aged 47 (× 400)

True malignant tumours of adipose tissue are rare. The best recent account of them is that of Stout, which contains some good examples and many references Most of them develop in middle aged or elderly people. The sexes are about equally hable. Trauma is of very doubtful influence in causation. The principal sites are the lower limb, retroperitoneal tissues and inguinal canal, but no site is exempt. Most liposarcomas of the limbs appear to arise deeply in intermuscular or intramuscular positions rather than in the subcutaneous tissues. There are several well attested cases of malignant change in pre existing benign lipomas (Adair et al., Stour).

(1) Structure

Liposarcomas show very variable rates of growth and degrees of histological differentiation and it seems probable that as with most other classes of tumours, sharp distinction between lipoma and liposarcoma is not always possible, and that borderline tumours occur Malignancy should be suspected if an apparently

Trauma was seldom noted in Adair and co workers' series or in my own series of 23 lipoma cases and Stout's 41 cases of liposarcoma gave no histories of significant trauma



(3) Structure

Many lipomas consist of fully mature fat cells arranged in lobules with a variable amount of supporting connective tissue and blood vessels. Two not unusual structural features however require special comment namely (a)

experimental production of tumours of adipose rather than of fibroblastic elements by carcinogens

TUMOURS OF ADIPOSE TISSUE IN ANIMALS

Lipomas are well known to occur in almost all kinds of domestic animals Feldman gives examples and eites many recorded lipomas in horses, cattle, swine sheep, dogs and birds. Of interest in showing points of similarity to human tumours are the instruces of multiple subcutaneous and intermuscular lipomas in horses the intestinal lipomas of horses, the congenital lipoma of the skull of a calf reported by McFadyean, the probably congenital lipoma of the brain reported by Kuhnau, and the large intracrantal lipoma in a hog extinuted by Feldman As in man, so in the larger animals lipomas may attain a large size. Feldman mentions a horse tumour weighing 42 kilograms. Microscopically, animal lipomas consist of mature fat cells or of mixtures of these with immature lipoblasts. Fibro lipomas with admixed fibrous tissue also occur. Feldman gives no specific mistances of liposareoma.

Rudduck and I collected the following lipomas from animals (a) a lipoma 10 centimetres in diameter and 450 grammes in weight, removed surgically from the subcutatious tissue of the perincum of a femile cattle dog 6 years old, (b) two lipomas one 45 centimetres and the other 8 centimetres in diameter removed surgically from the perincum of an adult female Pekinese. (c) a pedunculated ovoid subcutaneous lipoma 5 centimetres in main diameter, which had been growing slowly for 3 years on the inner aspect of the thigh of an adult parrot

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lipomatous tumour shows unusual variations of texture or colour and especially if it contains mucoid areas

Microscopic structure

This is very variable from fully differentiated adipose tissue cells to completely anaplastic cellular sarcoma and often includes also areas resembling myxoma or immature mesenchymal ussue. All cellular variants may be found in different parts of one tumour. Immature and grint lipoblasts showing all stages of vacuo lation are common. Fat stains applied to frozen sections will of course give the best pictures of the contents of mature or maturing cells. Sub divisions of lipo satcomas according to their microscopical characters is unwarranted. Stout gives good illustrations of the variety of structure and stresses the impossibility of histological sub division of the group. Murray and Stout describe the characters of malignant lipoblasts in tissue culture.

Certain features in the structure of lipomas and liposarcomas bear on the problem of the histogenesis of adipose tissue. We have scen—(a) that lipomas are often fibro lipomas, (b) that the fibromatous component may become a malignant fibrosarcoma (c) that the hipomatous component may become a malignant liposarcoma (d) that the structure of liposarcoma is highly variable and often includes mesenchyme like or mysoid tissue. These observations strongly suggest that while under normal conditions fat cells or their precursors may preserve their specialized functions and structure in pathological profiferations such as tumours they may display more diverse capacities for differentiation. Although tumours seldom appear to contain cells of transitional type between thoroblasts and lipoblasts it is nevertheless not unlikely that the proliferation in tumours may involve de differentiation of cells to a functionally indifferent level and their redifferentiation in part alone divergent lines.

(2) Multiplicity and metastasis

In view of the multiplicity of lipomas in some cases at is not surprising that liposarcourns also may be multiple and in some cases with multiple tumours, it has been debitable whether these were independent primary growths or metastases. Stout and Ackerman give examples of probable multiplicity and refer to others. Stegmund described a remarkable case of widespread liposar commitous tumours of the subcutts retropictioneal tissues mediastinum, bone marrow, and other parts in a woman aged 65, and he regarded the condition no doubt correctly, as a system descase of adipose tissue throughout the body.

Metistasis from liposarcomi certainly occurs however—to the lungs liver bones brain and other organs as in cases reported by Waldeyer Virchow Gernet, Nienhuis Jaffe Seids and McGinnis Eume and Stoit

(3) Experimental production of liposarcoma

Hateusen and k-rehbiel obtained liposartomas in a mouse and four guines pigs following subcutaneous injections of benzpyrene. Further experiments are needed to clueidate the local or constitutional conditions necessary for the

(2) Intermutability of cell-types in the skeleton

The intermutability of various types of cells of mesenchymal origin, already discussed in Chapter 41, must be re emphasized here. Skeletal fibroblasts chandro blasts, osteoblasts and osteoclasts are not distinct immutable species of cells, but can readily undergo metaplastic transformations one to another in many kinds of pathological states Indeed, some of these transformations take place normally or in simple repair, the formation of new bone by the fibrous periosteum and of cartilage by the perichondrium may be looked on as physiological metaplasias The structure of perichondrium is particularly notable in this respect, this membrane shows a gentle transition from fibrocytes to cartilage cells. Of course, extra skeletal connective tissues also can undergo bony or cartilaginous meta plasta, periostea and perichondria merely exhibit to a special degree this universal transformability of fibroblasts The reverse transformation-of osteoblast to fibroblast-is also a frequent one, displayed in many familiar lesions in which the fibrous replacement of bone takes place, as in the various types of "ostenis fibrosa and its congeners. In these lesions, the fibrous replacement is not effected by proliferation of pre existing fibroblasts to fill gaps left by departed bone cells, but by a progressive transformation of bone cells into fibrocytes When re ossification of this fibrous tissue ensues, as in a recovering case of hyper parathyroidism, the fibroblasts again become functional osteoblasts

We are too prone to think of osteoblasts and osteoclasts as distinct cells with distinct functions, rather than as functional variants of cells of the same type Where these cells, by virtue of ambient conditions, are functionally concerned in laying down new bone or in actively maintaining bone already there, they are osteoblasts, where, by virtue of ambient conditions they are functionally con cerned in bone resorption, they are osteoclasts. The osteoblast of to day may be an osteoclast to-morrow and vice versa, and this reversal of function probably amounts to no more than a slight alteration in the nature or quantities of the enzymes formed by the cells In lesions with fluctuating deposition and resorption, there are many cells of borderline or 'neutral 'appearance, which can be called "large osteoblasts 'or 'small osteoclasts" as one pleases

(3) Intermutability of cell-types in skeletal tumours

The transformations seen in the normal growth of the skeleton and in its non neoplastic disturbances are seen also in its tumours. While it is true that some tumours show exclusive or predominant differentiation of one or another type-osseous cartilaginous, fibrous or osteoclastic-others show divergent differentiation resulting in variable admixtures of two or more of these Chondromas ossify, cartilaginous or fibroblastic areas are found in osteogenic sarcomas, osteoclast like giant cells occur in osteogenic sarcomas and some tumours show the combined structure of osteoclastoma and chondroma In an inbred strain of mice with a high meidence of skeletal tumours, Pybus and Miller found all types and combinations of growths—osteomas, osteosarcomas, chondro sarcomas sphildle celled and giant celled tumours. Impartial survey of a collection of human skaletal tumours also shows the absence of sharp histogenetic subdivisions however necessary descriptive sub-divisions may be for clinical and

CHAPTER 43

TUMOURS OF CARTILAGE AND BONE

The Skeleton contains a variety of tissues, including not only cartilage and bone but also fibrous tissue adipose tissue, haemopoietic cells and undifferentiated reticulo endothelial elements. The fibroblastic adipose and haemopoietic tumours of the skeleton are dealt with in other chapters, here we are concerned with umours of osseous or cartilaginous tissue proper and with growths related to these. Before considering the particular kinds of tumours however, it is necessary to clarify certain general points regarding the structure and growth of the skeletal tissues and their tumours.

GENERAL CONSIDERATIONS

(1) The development of the skeleton

A knowledge of the normal development of bones and cartilages is essential to an understanding of their pathology including their tumours. Endochondral cossification, ossification in membrane periosteal bone formation osteoclastic resorption and modelling—all these familiar phenomena of normal growth have their counterparts in pathological growth. Hence, all that can be learnt of the normal development maintenance and metabolism of bone is sure to have a bearing on the pathology of its tumours. Indeed, it is quite possible that the causes of most skeletal tumours will be found to be not externally introduced careinogenic agents but disturbances of those factors on which the maintenance of bone depends—calcium and phosphorus vitamin D, parathormone and other hormones.

It is important to recall that the tissues of the skeleton do not attain maturity until adult life. Until the epiphyses unite endochondral ossification not essentially different from that of the foetus is still in progress. So also is periosteal ossification. This post nital persistence of skeletogenesis means persistence of foetal immaturity of the tissues and of their hability to malformations from interferences with their normal maturation. It is then theoretically possible that post natal as well as pre natal interferences may occasion heterolopic growth centres in epiphyseal or periosteal 'issue and lead to the formation of evostoses or to abnormal persistence or aberrant differentiation of masses of cartilage.

The rates of growth and maturation of different parts of the skeleton are of interest to the pathologist. Disturbances of growth are likely to produce their major effects in parts which are most actively growing at the time and the pathological effects are likely to show gradients of seventy corresponding to the growth gradients of the affected bone or of the whole skeleton if the disturbing factors are body wide. The distribution of many diseases of bone accords with this concept of greater susceptibility of the growing parts to injury. This applies not only to infections and deficiency diseases but also to tumours and tumour like malformations; including enchondromas, exostoses giant-cell tumours and osteogenic sarcomas.

erroneously described as "cystic" may be produced by many diseases, including metastatic growths, osteolytic primary sarcoma, plasmocytoma chondroma, osteoclastoma, other central non osteogenic tumours such as fibrosarcoma or liposarcoma, and localized fibrocystic disease (Willis, 1938 Fig 9, Grout, Figs 4-7)

(d) Confusion of primary and secondary multiple tumours

The radiographic appearances of multiple myelomatosis and of dis seminated carcinoma may be identical (Cosin, Willis)

Analysis of series of cases of bone tumours, the diagnoses of which have been based mainly on radiographic evidence, is valueless for pathological purposes

(6) Classification adopted

From what has been said, it will be clear that I am opposed to sub divisions of primary tumours of bone beyond those barely necessary, and that I regard even the main sub divisions adopted as arbitrary and of descriptive rather than histogenetic significance The multiple exostoses and enchondroses are malforma tions, which though not true tumours, must be considered in relation to their solitary counterparts and to true enchondromas and osteomas True enchon dromas and chondrosarcomas cannot be separated. nor indeed can a sharp line be drawn between these and osteosarcomas However, for descriptive purposes at least, it is convenient and useful to distinguish between predominantly cartil aginous and predominantly osteogenic sarcomas. The osteoclastomas form a fairly distinct group, which, however, as occasional malignant members and occasional members with combined chondromatous characters show, is not Reticulum cell sarcoma" may be an entity or a distinct completely isolated variant of primary sarcoma of bone, but too few cases have yet been investigated to warrant final conclusions "Ewing's tumour" must be discussed, not because it is an entity, but because the name is still used frequently and undiscriminatingly

We will consider the primary tumours peculiar to the skeleton under the

following heads

- Multiple enchondroses
- 2 Multiple exostoses
- 3 Solitary exostoses osteomas and osteochondromas
- 4 Solitary benign chondroma
- 5 Chondrosarcoma
- 6 Osteosarcoma
- 7 Osteoclastoma
- 8 Reticulum cell sarcoma of bone

To complete the list of possible primary tumours in bone, there must be added fibroma and fibrosarcoma, lipoma and liposarcoma, haemangioma chordoma, solitary plasmocytoma myelomatosis, myeloid leukacmia and Hodgkin s disease all of which are considered elsewhere. In this chapter brief mention will be made also of bony and carrilarinous tumours of soft itssues.

MULTIPLE ENCHONDROSES

I propose to say little of these rare malformations of the skeleton, for details of which the reader should consult the writings of Muller, Speiser, Stocks and

prognostic purposes The names employed denote different predominant types of differentiation but not necessarily different specific tissue origins

(4) Osteogenesis in non osteogenic tumours

Both pathologists and radiologists have often made the mistake of assuming that a tumour in which there is new formation of bone must be osteogenic. This fallacy is refuted by the osteoplasia and osteophytosis accompanying secondary carcinoma of bone and by the radiating osteophytes or parallel onion skin laminae of periosteal new bone in metastatic neuroblastoma (q v) These stromal reactions of bone and periosteum to invading non osteogenic growths are evident also in turnours of bone itself. In part at least, the regular radiating spines of new bone accompanying periosteum expanding sarcomas of bone and the new bony laminae set at an angle to the shaft where the expanded periosteum meets it a feature often visible in skiagrams are products not of the tumour tissue but of the expanded periosteum Brunschwig and Harmon (1935) studied these relationships in experimentally transplanted tumours in bone as well as in human material and concluded that much of the new bone seen in primary succomas of bones is indeed of non neoplastic periostical origin a conclusion in which I concur (Willis 1938) However in osteogenic sarcomas it is sometimes impossible to distinguish with certainty between neoplastic and periosteal new bone and indeed where the periosteum is itself part of the tumour formative field the distinction ceases to exist

(5) Limitations of radiographic diagnosis

Far too great a reliance has been placed on radiographic appearances in the diagnosis of tumours of bone. While these appearances often afford strong evidence of the nature of a tumour there are many possible fallncies. Experienced radiologists are well aware of these and are the first to deplore the prevalent assumption that radiologists possess clarivoyant powers for radiographic shadows. It cannot be too strongly missted that for purposes of precise diagnosis classifies toon and research microscopical study of adequate pieces of tumour is essential. There may be—there are of course—limits to the practicability of attaining this ideal in all cases. but in so far as it cannot be attained diagnosis must necessarily remain uncertain.

Possible errors in the radiographic diagnosis of bone tumours commented on in my 1938 paper and particularly dealt with by Grout include the following

- (a) The assumption that osteogenesis implies an osteogenic tumour.

 This has been dealt with above (see also Grout's figures 1 2 and 3).

 It is the main cause for mistaking secondary growths for primary ones.
- (b) Calcification may be mistaken for ossification

 Chondromas chondrosarcomas or chordomas containing calcified areas may be mistaken for osteosarcomas
- (c) Confusion of solitary lesions producing well circumscribed bone destruction.

 Circumscribed destruction producing radiographic appearances often

identified radiographically at birth and in infants. They progress at varying rates during the growing period, during which they possess growing caps of cartilage which undergo ossilieation part passu. When growth of the skeleton ceases. the exostoses also cease to grow, and their cartilage cans become either completely ossified or reduced to a thin quiescent zone. The exostoses are not superimposed on the cortex of the bone but represent outnouchings of it with spongy bone In addition to the grossly obvious exostoses, affected bones show innumerable tiny exerescences and irregularities and often excessive width and abnormal contours Diminished stature, bodily asymmetry or other deformaties are sometimes present. The lesions tend to be symmetrically bilateral and are usually largest and most numerous in justa epiphyseal parts of long bones, especially at the ends where main growth occurs, namely, the lower end of the femur, upper ends of tibia and fibula, upper end of humerus, and lower ends of radius and ulna But the distribution varies greatly, and any chondral bones may be affected. In a high proportion of cases, about two thirds, there is a definite family history of the disease. Stocks and Barrington found that in most cases inheritance was through an affected parent, the fither about thice times as frequently as the mother Transmission sometimes occurred through an unaffected female but apparently not through an unaffected male. About two thirds of the subjects with multiple exostoses are males

The disease is electly a general disturbance of ossification in cartilage bones. Controversy as to whether this disturbance affects chiefly the periostea or the epiphyseal cartilages is I think, pointless Keith's concept of a general defect of

modelling of the bones (diaphyseal relasis) can embrace both

Chondrosarcoma supervening on multiple exostoses

One of the first reports was that of Weber (1866), who described a man of 25 years with multiple exostores and 1 large chondrostreoma of the pelus which had invided the iliac vein and produced cartilaginous emboli in the pulmonary arteries. Infle reported 3 cases of chondrostreoma in his series of 28 cases of multiple exostoses (11 per cent) but pointed out that since most of these patients were children or adolescents and since sarcoma usually does not superveine until adult life (at 25, 28 and 36 years in his 3 cases) the final proportion of cases to develop sarcoma must certainly be greater than 11 per cent. However, sarcoma does occasionally develop even during childhood, e.g. at the age of 10 years in Bennett and Berkheimer's case.

Streams supervening on multiple exostoses appear always to be chondro sarcomas usually of the well differentiated gelatinous type apt to be microscopic ally diagnosed as soft "chondrom" (see below). These tumours are often of slow growth they may grow to huge sizes locally without metastrisizing as in Jiffe s'second case of 13 years duration or they may invade veins and disseminate

to the lungs and elsewhere, as in Weber's case

SOLITARY EXOSTOSES OSTEOMAS AND OSTLOCHONDROMAS

Solitary trowths generally similar in structure to those of hereditary multiple exostoses are the commonest tumours of the skeleton. Like the multiple lesions,

Barrington Cole, Hunter and Wiles and Jacobson The disease variously known as "multiple enchondromatian enchondromatis". dyschondroplasia " (Ollier), and "chondrodysplasia is characterized by the presence from an early age of masses of cartilage within many or all of the cartilage bones of the body especially of the limbs. The lesions may be symmetrical or asymmetrical and they vary considerably in their bulk and the degree of deformity they produce. There is no justification for separating as "Ollier's disease only cases showing asymmetry even though the cases described by Ollier were of this kind.

Speiser's full necropsy study of this disease in a boy of 4 years showed that many of the masses of cartilage within the diaphyses of long bones had pedicles of attachment to the epiphyseal cartilages, but that others were unrelated to these and arose from islands of cartilage in the periostea. These findings show that the controversy as to whether the 'chondromas arise from the epiphyseal cartilage or periosteum is pointless they arise from both as a result of some general disturbance of ossification in cartilage. The presence of periosteal islands of cartilage in this disease similar to those described by Muller and others in cases of multiple exostoses suggests a relationship between the two diseases, and some writers have assumed that they are but different manifestations of one disease. There is very little real evidence to support this view. With rare and doubt ful exceptions patients show either exostoses or enchondroses and not both (Jaffe), and while a familial incidence obtains for the majority of cases of multiple exostoses this is exceptional in cases of pure enchondromatosis (Stocks and Barrington Jacobson) The supposition that the two diseases are related and that they are seen in combination in individuals and in families appears to be in part at least due to incomplete observations

With the lapse of time most of the cartilaginous masses in patients with enchondromatosis become quiescent and they may undergo regression or ossification. But some during or after the period of normal growth of eartilage continue to grow excessively as true chondromas or chondrosarcomas (references by Hunter and Wiles). It is difficult to deny the neoplastic quality of the huge multiple masses of cartilage which develop in the hands and feet and elsewhere in some cases (figures of which are reproduced by Stocks and Barrington). Typically and essentially however enchondromatosis is a dystrophic and not a neoplastic disease. (Jacobson) Speiver advanced reasons for believing that the initial disturbances leading to this disease operate between the fourth

and eighth months of foetal life

MULTIPLE EXOSTOSES

This familiar disease designated also multiple ossifying chondromata diaphyseal aclasis (keith) and hereditary deforming chondrodysplasia (a vague clumsy name) also calls for no more than summary treatment here Details will be found in the papers of Muller Keith Stocks and Barrington Jacobson and Jaffe

Like enchondroses multiple exostoses are malformations not neoplasms. Although they are often not discovered until later childhood or adolescence they probably take origin in most cases during foetal life for they have been

particularly stressing the histological features which suggest malignant properties, and also the grounds for distinguishing between chondrosarcoma and osteo sarcoma

(1) Age and sex

On the average, chondrosarcomas arise much later in life than osteosarcomas Most patients are between 30 and 50 years old, and children are rarely affected The sexes are about equally hable

(2) Site and pre-existing lesions

The long bones of the limbs, the pelvis and the ribs are the most frequent sites. In roughly equal numbers of cases, the initial site of the tumour is central within a bone or springing from the surface of a bone or cartilage. In a small proportion

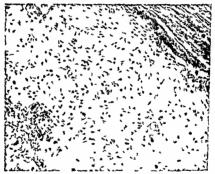


Fig. 328—Chondrosarcoma of upper half of humerus in a man of 41 years. At first diagnosed as a beingn chondroma, the tumour recurred and metastasized to the lungs. (\times 60)

of cases of central chondrosarcoma, this has supervened on a pre-existing supposedly benign enchondroma or enchondrosis. In a much larger proportion of cases of external chondrosarcoma of bone this has arisen from a pre-existing cartilaginous exostosis or osteochondroma (Lichtenstein and Jaffe). There is insufficient evidence to incriminate trauma or any other specific factors in the causation of chondrosarcoma. The commonest of all cartilaginous tumours those of the phalanges and metacarpals, are very rarely malignant, but a case with metast uses was reported by Cruickshank.

(3) Structure

Some chondrosarcomas show plain histological evidence of malignaney cellular pleomorphism multinucleated cells areas of spindle celled growth and autotic figures. Others consist wholly or mainly of well differentiated often soft mucoid cartilaginous tissue microscopical study of which does not suggest the solitary ones develop chiefly in young people, and affect chondral bones especially in juxta epiphyseal parts, and especially the lower end of the femur or the upper end of the tibia

The solitary growths are so similar to multiple exostoses in most respects, that there can be little doubt that they arise from a similar kind of developmental disturbance. In most cases however, this disturbance must be purely local for the remainder of the skeleton is normal and there is no clear evidence of an hereditary predisposition. Cases of apparently solitary exostosis are reported in families with multiple exostoses, but it is probable that complete examination



Fig. 327 -- Case 1 Benien asteoid tumout of skull (x 120)

of the skeleton in such cases would reveal other inconspicuous growths. Despite their similarity, then, the solitary growths should be regarded as distinct from the multiple ones and not merely as localized manifestations of the multiple disease This distinction is all the more pertinent because the solitary growths not infre quently continue to grow after cessation of general prowth of the skeleton thus showing their genuinely neoplastic character and their rightful claim to be called exostosis ' osteoma or 'estenchandroma rather than However the line of separation between neoplasm and malformation cannot be drawn with precision nor can we always distinguish between the strictly solitary growth and the seemingly solitary one which is the only manifestation of the hereditary discuse. It is not unusual for a solitary osteochondroma to give origin to a chondrosarcoma

Osteochondromas of the base of the skull are particularly described by List The rare ' wory osteomas of the skull and facial bones form a peculiar group, the exact limits of which however it is difficult to define. When we have eliminated from the osteoma group—m which formerly they were often placed—such lesions as hyperostoses due to invading meningiomis localized ✓ forms of leontiasis (the nature of which is still unknown) inflammatory

te one-half of all tumours were close to the knee joint a proportion nearly identical with that in Christensen's series. Thus, the sites of predilection are, like those of exostoses and osteochondromas as well as of osteoclastomas, the ends of the long bones "where the growth period is longest, and the growth momentum is greatest" (Christensen). When a sarcoma arises in a bone with an ununited epiphysis, the primary site is in the diaphysis, primary epiphyseal sarcomas are excessively rare.

(3) Causation

The age and site incidence of osteosarcomas strongly suggests that theicausation is to be sought mainly in disturbances of bone growth and maturation. This suggestion is supported by the analogous fact, already noted, that developmental enchondroses and exostoses certainly predispose to supervening chondro sarcoma, and by the occasional supervention of osteosarcoma in cases of fibrous dysplasia of bone (Albright's disease), as noted by Jaffe (1946). It must be noted here, however, that Albright's disease may itself produce large fibrous and cystic tumour-like masses which are to be regarded not as true neoplasms but as hamatromas.

(a) Extrinsic carcinogens

In only a very small fraction of cases of osteosarcoma is there evidence of extrinsic physical or chemical causative factors Indeed, the only cases in which an extrinsic agent has been proved culpable are those due to absorbed radio active substances, as described in Martland's account of occupational osteo sarcomas in watch dial painters These tumours developed in young people after relatively brief periods of exposure Thus the ages at necropsy of 5 cases reported by Martland were 20, 27, 30, 33 and 34 years, and the times of occupa tional exposure to radio active material were between one and five years. The tumours were multiple in 3 of the 5 cases and the sites included femur, scapula, vertebrae, pelvis and skull Absorbed radium and other radio active elements accumulate in the skeleton and set up a chronic radiation osteritis and the evidence is clear that the sarcomatous change supervenes in areas of bone so affected. In cases of chronic poisoning by radio active substances, all but a minute fraction of the retained material is found in the bones Chapter VII of Hueper's book contains an excellent outline of poisoning by radio active substances and of the osteosarcomas caused by them The experimental production of bone sarcomas by means of radio active substances (see Chapter 4) has confirmed and amplified our knowledge of these tumours

(b) Trauma

Injury has often been regarded as a cause of sarcomas of bone but the evidence is inconclusive. There do occur occasional cases, like that reported by Webster, in which surcoma appears a few months or years after the infliction of an injury to the bone at the particular site but it is doubtful if these infrequent cases exemplify more than the laws of chance. The bones of all mankind receive frequent injuries, mild and severe, osteosarcomas are relatively rare tumours, the numerous fractures of modern life are very rarely followed by sarcoma, the great majority of cases of sarcoma give no clear history of trauma, and in not a

sarcomatous properties As Lichtenstein and Jaffe insisted however thorough search of adequate material from such growths will often reveal areas with suspicious cellular atypism. Yet there are tumours the structure of which in both primary growth and metastases is indistinguishable from that of benign chondromas (Fig. 328)

(4) Spread and metastasis

Many chondrosarcomas grow slowly remaining only locally invasive for years. Some tumours, however invade veins and metastasize to the lungs. Very extensive growth within large veins has been described by many writers or g by Weber Ernst. Fry and Shattock, Kosa Phemister and Warren. The tumours described by Fry and Shattock and by Kosa extended in continuity through the inferior vena cava and the right side of the heart into the pulmonary arteries. Blood borne metastases elsewhere than in the lungs are unusual, but have been reported in bones (Recklinghausen, Martin) adrenal and heart (Lichtenstein and Jaffe) skin (Cruickshank), etc.

OSTEOSARCOMA

Osteogenic sarcomas—or more simply osteosarcomas—are those in which tumour parenchyma displays recognizable differentiation of bone or osteoid tissue. As already pointed out the formation of new bone by expanded periosteum may be mistaken for bony differentiation in the tumour itself. But admitting this source of error it is still clear that many—indeed most—ascromas of bone of osteoid tissue for these are often recognizable in extra periosteal extensions of the growths or in their metastases. A few sarcomas of bone are undifferentiated spindle celled or pleomorphic celled growths not microscopically identifiable as of bony origin. In my opinion sub division of the osteosarcomas into periosteal medullary sclerosing telangied tatic etc. are artificial and unjustifiable. These adjectives do not denote distinct types of growth but merely variants of the one type.

(1) Age and sex

Christensen s analysis of 441 cases of bone sarcoma of all types (mainly of course osteogenic sarcoma) reveals the main features of age sex and site incidence of this disease. Males are affected decidedly more frequently than females in a ratio of about 60 to 40 per cent. The greatest number of cases occurs in the second decade e.g. 40 of 80 cases reported by Badgley and Batts. nearly two thirds of all patients are between the ages of 10 and 30 and one third of them are over 30 years. Very young children and old people are seldom affected.

(2) Site

Christensen's figures showed that of the total of 441 tumours 287 (65 per cent) were in the lower limbs including 174 in the femur (162 at its lower end) and 83 in the tiba (69 at its upper end) 72 (16 per cent) were in the upper limbs, including 54 in the humerus (31 at its upper end) and 82 (19 per cent) were in the bones of the head and trunk the commonest single site being the scapula In Badgley and Batts's 80 cases there were 25 timours of the lower end of the femur, 11 of the upper end of the tibua and 4 of the upper end of the fibula

of the retention of function by neoplastic osteoblasts is afforded by the high alkaline phosphatase content of osteosarcomatous tissue, the great increase in the amount of this phosphatase in the sera of patients with osteogenic sarcoma its fall following removal of the tumour, and its further rise with the development of recurrent growth or metastases (Franscen and MeLean)

(5) Metastasis

The major risk of osteosarcoma is early metastasis to the lungs Pulmonary metastases eventually develop in a high proportion—at least three quarters—of all cases Radiographic evidence of these should be sought in all eases prior to treatment of the primary growth, and again at intervals following amputation. In the majority of eases metastases appear within 2 years from the onset, but they may do so after much longer intervals eg 13 years in one of Badgley and Batts's eases. Speed reported a remarkable case in which in spite of clear tadio graphic evidence of pulmonary metastases, the patient remained alive and well after 13 years the shadows of the metastases having remained almost unchanged, without any treatment, for about 10 years.

Blood borne metastases sometimes appear in parts other than the lungs, e.g. in the skin (Sequira and Turnbull Finnerud, Brunschwig and Harmon), in other bones (references in my 1934 work) in the liver or brain (Harding and Courville) Metastases in lymph glands are unusual (references in my 1934 work, Brunschwig and Harmon, 1933 Crise I. Warren and Meyer)

OSTEOCLASTOMA

(Giant cell Tumour of Bone)

(1) Histogenesis and nomenclature

The changing views regarding the nature of this tumour have resulted in a diverse and confusing terminology—' myeloma , "myeloid sarcoma', 'tumeur a myeloplaxes , ' benign giant cell tumour", 'osteoclastoma', and 'chronic (non suppurative) hemorrhagic osteomyelitis', being only some of the name applied to it. Myeloma and myeloid' should be discarded for the tumours are unrelated to the haemopoietic tumours of bone marrow and in particular are quite distinct from the lesions of myelomatosis. Nelaton s' tumeur a myeloplaxes was erroneous the tumour giant cells are certainly not megalarjo cytes' Giant cell tumour' is a saisfactory non committal name as long as it is not allowed to lead to confusion of this tumour with giant c.lled osteosarcomas, and as long as it is not preceded by 'benign' Barrie's concept of "chronic hemorrhagic osteomyelitis" is deservedly moribund, its falsity was promptly exposed—too leniently I think—by M J Stewart (1922), and such a flimish piece of speculation should never have been advanced not taken seriously

The view that the tumour is an osteoelastoma was suggested in 1922 by Stewart and later adopted by most British pathologists. I find myself, after an initial period of doubt regarding the validity of this view, a convert to it. The close structural similarity of the tumour giant cells with the larger osteoelasts in bone resorptive lesions the identical appearance of the tumour tissue and of the intra cystic masses of mingled fibroblastic and osteoelastic tissue in

few cases in which trauma is claimed as causative the sequence of events shows that the tumour must have been already well established at the time of the injury. These facts together make it clear that trauma either plays no part at all or only a very infrequent one, in the causation of bone tumours. We will continue to be struck by occasional remarkable coincidences and courts will continue to allow compensation claims for allegedly traumatic sarcomas of bone, but the only attitude for scientific pathologists is one of stringent scepticism.

(c) Ostestis deformans

This disease unquestionably predisposes to osteogenic sarcoma osteogenic sarcomas arising after the age of 50 years are in people with Paget s disease Paget himself was the first to record eases of this association and many subsequent examples have been reported Indeed cases of this kind are far from uncommon most surgeons radiologists and pathologists are familiar with them The exact proportion of cases of Paget's disease to develop sarcoma cannot be clearly estimated because mild degrees of the former disease are much commoner than gross readily diagnosed lesions. The risk of sarcoma in Paget's disease is certainly less than suggested by Paget's own series in which 3 of 5 patients had sarcoma Perhaps 5 or 10 per cent of patients with easily detectable clinical or radiographic signs of osteitis deformans may be expected to develop sarcoma Most of the tumours are clearly osteogenic but a few of them appear fibro sarcomatous or cartilaginous. They arise most frequently in the long bones of the limbs especially the femur, humerus and tibia, but occur also in the scapula clavicle pelvis or other bones. A prevalent view that they never arise in the skull is erroneous. Kirschbaum described such a case and referred to 8 others Albertini made the interesting observation that the sarcomatous change took place multifocally or diffusely in fibrous areas of the affected bones

(4) Structure and growth

I propose to say nothing of the gross and little of the microscopic structure of these tumours. They have been fully described and depicted in many pathological surgical and radiological treatises and papers. Suffice it to say that their microstructure ranges from that of fully differentiated compact bone to anaplastic opinide celled or pleomorphic celled growth devoid of recognizable osteoblastic differentiation and that a single tumour sometimes shows a wide range of differentiation. Cellular anaplastic tumours often show patchy differentiation of uncalcified disorderly osteoid tissue which permits their histological recognition (see Figs. 302 and 332-334). Great cellular pleomorphism, with mixtures of spindle cells and gaint cells containing a few or many nucleus a frequent feature Sometimes the giant cells resemble those of the osteoclastoms and it is tempting to suppose them to be neoplastic osteoclasts. But proof of this is difficult because multinucleated giant cells are found in many kinds of anaplastic tumours. In Cass III below, however the tumour contained many typical osteoclasts.

The osteoblastic nature of the surcoma cells is clearly displayed in cases in which metastatic growths show osteoid or bony differentiation. In 1934 I referred to many records of such metastases and additional examples were reported by Brunschwig and Harmon (1933) and Harding and Courville (1934). Evidence

commonest sites, in order, are—distal end of femur, proximal end of tibia, distal end of radius, proximal end of humerus, distal end of ulna and proximal end of fibula. The remaining 25 per cent of the tumours affect the bones of the head and trunk, especially the pelvis and vertebrae. Lord and Stewart (1943) give reference to the rather rare records of ostcoclastomas of the skull. It has been stated that giant cell tumour frequently starts in or predominantly involves an epiphysis, and it has even been suggested that it should be called "epiphysical giant cell tumour." This idea has arisen because of the striking predilection of these growths for the extremities of the long bones, but in the strict sense it is not correct. An ostcoclastoma in a young bone with a still unfused epiphysis is situated, not in the epiphysis, but in the metaphysis, and the epiphysial line is intact, as in the cases in children reported by Stewart and by Burland and Harries.

(3) Structure

(a) Naked eve appearance

This varies greatly Young healthy tumours are uniformly red, brown or sometimes grey or even white, soft and frable Older tumours become variegated by areas of fibrosis, cysts, haemorrhages, pigmentation, yellow necrosis, or calcification Early expansion of the bone is usually fairly uniform in all directions, but it may later become irregular and eccentric. A prevalent impression that the radiographic appearances of osteoclastomas, especially the multilocular or soap-bubble." appearances, are distinctive and "typical" is erroncous, the same appearances can be produced by other expanding non osteogenic tumours.

(b) Microscopical structure

The micro structure of healthy parts of the growths, unaftered by secondary changes, is characteristic. The admixture of spindle cells and multinucleated giant cells, the latter often distributed rather uniformly throughout the tissue, is unlike that of any other bone tumour. The giant cells measure 50 to 100 μ or more in diameter, have processes which appear to anastomose with those of the spindle cells, and possess as many as 20 or 40 nuclei each in a single section. These nuclei are identical in appearance with those of the spindle cells, and there are appearances of the fusion of the latter to form the giant cells appearances interpreted however by some writers (e.g. Burland and Harries) as a fissuring of the giant cells to form spindle cells. Motton figures may be found in small numbers in the spindle cells, but are rarely, if ever, found in the giant cells. The viscularity varies greatly, the viscular channels are thin walled and the tumour cells abut closely on them. Except where secondary fibrosis has occurred, collagen fibres are sparse, and there is no good reason for dubbing the spindle cells. 'fibroblasts' Occasionally, lipoid laden foam cells are plentiful in parts of the growth

(4) Behaviour

In the great majority of cases of osteoclastoma with more or let's characteristic clinical and histological findings, the tumours pursue a benign course, i.e. they grow slowly, do not transgress the periosteum, do not metastasize and are curable by adequate local removal. As Stewart insisted however incomplete removal of a genuine osteoclastoma, especially by eurettage, is followed by recurrence, and some tumours do transgress the bone cortex and periosteum and invade surrounding muscles and other tissues. Lord and Stewart described an

hyperparathyroidism (these masses are often called osteoclastomas, for this very reason) and the conspicuous bone resorptive effect of the tumours, together constitute conclusive evidence that these growths are indeed osteoclastomas

Those who, like Jaffe et al (1940) object to this view and prefer the histo genetically neutral name grant cell tumour' do so for three reasons First, they can scarcely concerne of a genuine neoplasm in which skeletal phagocytes are an essential element -to which it may be replied that phagocytes are not exempt from tumour formation and that in any ease osteoclasts are not phagocytes Secondly they say the giant cells of the giant cell tumor while resembling, also show definite differences from indubitable osteoclasts ' -to which I reply that on the contrary the resemblance is so close as strongly to suggest their Thirdly it is contended that the spindle cells of the tumours are the essential tumour cells and the giant cells are only fused aggregates of these .- the reply to which is that this does not exclude their osteoclastic nature for normal osteoclasts are formed by syncytial fusion of fusiform and stellate mononucleated cells (see Dawson and Struthers's execulent account 1923) The precise origin of these mononucleated cells-whether from fibroblasts, vascular endothelium or osteoblasts-is beside the point. From what we know of the normal development of ostoeclasts we would expect a tumour of osteoclasts to show a mixture of unfused pre osteoclasts and more differentiated multinucleated syncytia, and this is just what our osteoclastoma shows

In my opinion then there is little doubt that the giant cell tumour of bone arises from and consists of bone formative (as opposed to marrow) cells which possess the attributes of osteoclasts I say bone formative cells deliberately because it is notifier necessary to assume nor likely that osteoclasts are an immutable self perpetuating species of cell. As already pointed out it is much more probable that osteoblasts and osteoclasts are merely reversed functional phases of cells of the one kind which we can conveniently call bone formative cells. An ost-oclastoma is a tumour of these cells in which the functional bias is osteo clastic rather than osteoblastic.

(2) Age, sex and site incidence

(a) Age

Most large series e.g. Christensen s, show that more than two thirds of the tumours develop between the ages of 10 and 30 years the greatest number of cases being in the third decade. Young children and the elderly are rarely affected is it only a coincidence that the pale osteoclastomas reported by Stewart (1922) and Burland and Harries (1924) were both in children?

(b) Sex

Males and females are about equally affected e.g. 170 to 192 in Christensen's series

(c) Site

As Christensen's figures show about three quarters of the tumours are in the limb bones—about one half of them in the lower and one quarter of them in the upper limbs—and with rare exceptions they are at the ends of the bones. The

shows, I think that osteoclastomas are not invariably benign, that some of them, not initially distinguishable from their benign fellows, invade and metastasize, and that this malignant behaviour does not picsuppose supervening sarcoma in a benign tumour, but is a property of certain members of the class ab initio

(5) The chondromatous grant-cell tumour

Codman described 9 cases of "chondromatous giant cell tumor" of the upper end of the humerus, and regarded these as a variant of the ordinary giant cell tumour Jaffe and Lichtenstein (1942) disputed this interpretation and held the growth to be a special form of "benign chondroblastoma" in which groups of multinucleated giant cells are incidentally found. However, the tumour in the following case supports Codman's views

Case II—(Mr E W T Morris x case)—History—A male Sudances aged 25 had noticed gradually increasing swelling of lower end of right tibia for several years X ray appearances were those of giant cell tumour. The excised part of the tibia contained a tumour 8 centimetres in diameter distending and replacing the bone and consisting of firm cartilagenous tissue. Histology (Fig. 329)—Giant-cell and spindle cell tissue is mingled with a cartilagenous matrix. The tumour is simultaneously an osteoclastoma and a chondroma. Its cartilage cells are the same cells as the osteoclastoma cells for everywhere there are gentle transitional forms between typical cartilage and areas of typical giant cell tumour. (Dr. H. A. Sissons is making, a thorough study of this specimen.)

The structure of the tumour, which is very different from that of Jaffe and Lichtenstein's "benign chondroblastoma", favours the view of Dawson, Innes and Harvey that the giant cell tumour probably takes origin from a plum potential cell with capacities for differentiation other than into osteoclasts, or alternatively, that proliferating osteoclasts and chondroblasts can undergo mutual metaplastic transformation

(6) Lesions simulating osteoclastoma

Masses of tissue with a structure closely resembling that of osteoclastoma, and often designated as such, are found in the bones in generalized osteitis fibrosa (hyperparathyroidism) and also in some of the lesions of localized osteitis fibrosa These masses are not true tumours, and should not be called such, even when they attain large sizes as in Mathers and Cappell's case, they have no powers of independent progressive growth but retrogress when the bone re forms Dawson and Struthers did much to correct the mistaken identification of giant celled areas in local or generalized osteriis fibrosa as "myeloid sarcomas correlated mistake of supposing giant cell tumours to be manifestations of localized osteitis fibrosa They pointed out that the one represents a limited response of the tissues to the requirements of bone resorption, while the other is a progressively growing neoplasm. The close structural resemblance of the two tissues-neo plastic and non neoplastic—is no more surprising than the close resemblance of some chondromas to normal cartilage or of some areas of osteosarcomas to the osteoid tissue of healing callus At the same time, the very fact that giant-cell tumour tissue can perfectly resemble reactionary osteoclastic tissue is itself good evidence that the former is indeed osteoclastoma

osteoclastoma of the temporal bone which projected as polypi into the external ear, invaded the transverse sinus and directly infiltrated the cerebellum. There are now many reports of otherwise typical giant cell tumours which have metastasized to lymph glands lungs or other parts (references by Willis 1934 also Korchow and Jaffe et al) King and Jaffe et al have attempted to correlate the degree of cellular atypism in individual tumours with their prognosis

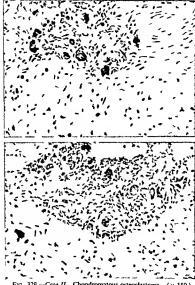


Fig 329 -Case II Chondromatous osteoclastoma (× 150)

Several writers have suggested that when a giant cell tumour runs a malignant course this is due to supervention of sarcomatous change in a formerly benien tumour, and have pointed to the usually anaplastic structure of the metastases in these cases But of course the phenomenon of increased anaplasia with metastasis is well known in many kinds of tumours and in some of the metastas izing osteoclastomas e g those of Finch and Gleave and of Dyke the structure of the metastases did not depart for from the benign type. The evidence

both mycloid and fibrous, are not tumours but granulomas, they are non invasive, often do not recur even after incomplete removal, and sometimes retrogress spontaneously. Rarely, true tumours—osteoclastomas or fibrosar comas—may arise from the jaw or its periosteum but these should be distinguished from the ordinary non neoplastic epulides.

The giant celled tumours of synovial tissues, discussed in the next chapter,

also should not be confused with osteoclastomas

RETICULUM CELL SARCOMA OF BONE

Under this title, Parker and Jackson (1939) segregated a group of 17 non osteogenic tumours of bones, which had earlier been diagnosed variously as Ewing s sarcoma, Hodgkin s disease, lymphosarcoma, etc. The tumours affected males and females about equilty, occurred chiefly in the second, third and fourth decades, but also in older age groups and were situated most frequently in the femur, claviele, tibia and humerus. They formed large painful destructive growths, sometimes producing pathological fracture, and devoid of distinctive radio graphic appearance, and they gave a variable response to radiation, some responding well but recurring, others not responding at all. Microscopically they consisted of rather pleomorphic rounded or polyhedral cells larger than lymphocytes, with some reticulum fibres between the cells. Although no necropsies had been performed, it was unlikely that these growths were metastatic, since they pursued a relatively benign course and 7 of the 17 patients were well 10 years or more after amputation. Confirmatory reports have been published by other workers, e.g. by Szutu and High (1942)

In spite of the paucity of necropsy studies there are good grounds for accepting the existence of a non osteogenic sarcoma of bone with rather distinctive character. There is no doubt that in the past radio sensitive members of this group of tumours have often been called 'Ewing's sarcoma' But, as Parker and Jack son pointed out, the reticulum cell sarcomas should be distinguished from 'Ewing's tumours' for their age incidence, massive bone destruction, relatively good prognosis and variable response to radiation, are unlike the original Ewing syndrome, and their lustology also differs from that of 'Ewing's tumours' as usually described

Needless to say great care should be exercised in making a diagnosis of reticulum cell sarcoma of bone. There is risk that the errors committed in the past under the captions "endothchoma" and "Ewing's tumour—the errors of including diverse kinds of growths, especially metastatic ones—may be repeated under this new title. The micro structure of reticulum cell sarcoma is not patho gnomonic, but could be simulated by anaplastic carcinoma lymphosacoma and other tumours. Each individual tumour must be weighed on its ments and finally diagnosed as reticulum cell sarcoma only when all the evidence, clinical and pathological, compels this conclusion. It remains to add that the presses histogenessis of the tumour is still sub judice, but the name "reticulum cell sarcoma" can be accepted pending further studies of well authenticated growths of this kind.

EWING S TUMOUR

Too much ink has already been spilt in controversy on this chaotic subject, and I cannot undertake here a detailed critical review of its huge and confusing

Myeloid epulis ' (Figs. 330, 331) should not be grouped with the osteo clastoma of bone for again resemblance does not denote identity. In many

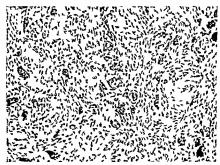


Fig. 330 -Myeloid epulis (× 120)

epulides the giant celled tissue is clearly only a form of inflammatory granulation tissue containing extravasated blood pigments—all transitions between ordinary

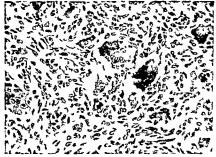


Fig. 331 -- Myeloid epulis (< 300)

granulation tissue and giant-celled tissue are found. The giant cells are often smaller and less regular than those of osteochstom variable in number and they often contrin phygocyted hiemosiderin. With few exceptions epulides

- Huge chondrosarcoma of nasal cavity of cocker-spaniel aged 6. no metastases
- Mixed carcinoma osteosarcoma of thyroid gland of sheepdog aged 10, with ostcosarcomatous metastases in lungs (Rudduck and Willis, Case VIII. and see Figs 301, 302, Chapter 36)

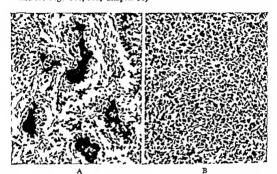


Fig. 334 - Detail of Fig. 333 A = well differentiated bone trabeculae B = undifferentiated part of growth (x 120)

(2) From other animals

- Large chondrosarcoma of upper half of humerus of cat aged 16, with metastases in lunes
- Chondrosarcoma of ribs of a sheep, with metastases in lungs 11

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literature To some extent this has already been done in previous papers (Colville and Wills 1933 Wills 1938 and 1940) I have read also many accounts of 'Ewing's tumours other than those there reviewed including those of Rix and Geschickter, Geschickter and Masentz Potozky and Freid, Foot and Anderson Gharpure and Lichtenstein and Jasse (1947) The following are my conclusions

- (1) Ewing s tumour is not a pathological entity it is merely a (rather ill defined) syndrome of a non osteogenic round celled, radio sensitive tumour in a bone usually a long bone usually in a young subject and usually causing diffuse elevation of the periosteum. This syndrome can be caused by several different kinds of tumours
- (2) In the majority of cases heretofore diagnosed as Ewing s tumour the tumours have been metastatic
- (3) So called Ewing s tumours in children and adolescents are usually metastatic neuroblastomas
- (4) Primary reticulum cell sarcoma accounts for a minority of reported Ewing s tumours

The evidence for (2) is given in my earlier papers and in Carl Sternberg's last paper (1935). The evidence for (3) is given in Chapter 55 of this book, and I have also to record that several workers have written to me to say that in recently reviewing their Ewing's tumours they have found some of them to be neuro blastomas. It is significant too that Rix and Geschickter head a section of their paper on tumours of the spine——Sympathicoblastoma (and Ewing's sarcoma) and that they conclude No typical Ewing sarcoma of the spine was found in the present series, and the tumors previously classed as such were thought on further study to be sympathicoblastomas. In their paper on 135 Ewing's sarcomas. Geschickter and Mascritz stated Neuroblastoma was found to resemble Ewing's sarcoma clinically and microscopically Both tumors respond to irradiation. The presence of rosettes and neurocytes are distinctive histo logical features of neuroblastoma. I also believe that neuroblastoma rosettes are distinctive, and in my opinion the rosettes in Ewing's tumours' depicted by F W Stewart Foot and Anderson and Gharpure show these almost certainly to have been neuroblastomas.

A radio sensitive reticulum cell sarcoma occurring in a young person might qualify for the Ewing syndrome and there are some workers who like Stoud feel unable to separate reticulum cell sarcoma and Ewing's tumor. Most workers however, for the reasons given in the preceding section agree that in general reticulum cell sarcomas do not resemble 'Ewing's tumours' as commonly described and that the former should be segregated out of the heterogeneous dumping ground which the latter has become. When we have removed from this dumping ground many metastate neuroblastomas some metastate lymphosarcomas and other secondary tumours which it has been admitted have been placed there occasional non ossifying osteogenic sarcomas which have also been wrongly cast there and occasional radio sensitive reticulum-cell sarcomas more or less fulfilling the Ewing criteria, then there will probably be nothing left in the dump.

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BENIGN SYNOVIOMA

(1) Age, sex and site incidence

These not uncommon tumours arise in young and middle aged adults, they rarely appear in children or old people. The multiple form in joints which are the seat of hyperplastic synovitis is more common in men than in women, but the reverse applies to the solitary synoviomas of tendon sheaths.

Solitary tumours are commoner than multiple ones, and arise from tendon sheaths much more often than from joints or bursae. Multiple tumours are much commoner in large joints than in tendon sheaths, the knee joint is by far the most commonly affected joint. The commonest sites of solitary synoviouss of tendon sheaths are in the hands, especially the fingers, the feet are less often affected and other sites are rare. The flexor tendon sheaths are affected much more often than the extensor. The tumours grow outward from the sheath and rarely project into its cavity or involve the tendon. The right hand is affected more frequently than the left, a difference which has been held to indicate trauma as a causative factor.

(2) Neoplasm or granuloma?

The view that the "xanthomas" and giant cell growths of synovial membranes are not true tumours but inflammatory granulomas was advanced in 1913 by Fleissig and has recently (1941) been strongly upheld by Jaffe, Lichtenstein and Sutro, who summarize this opinion in the title "pigmented villonodular synovitis". There is no doubt that the widespread brown seaweed-like synovial growths sometimes found filling a large joint are inflammatory and not neoplastic, and that these often include small or large nodules closely resembling in structure the solitary giant cell growths which are usually regarded as tumours. On the other hand, from the general structure cellularity and mitotic activity of many of the solitary growths it seems clear that they are indeed neoplasms. Many of these have the structure of more or less cellular fibromas, with few or no giant cells and foam cells and little or no pigment, and miny of them appear to be isolated growths from synovial membranes devoid of any signs of generalized villous synovitis.

However, this seeming contradiction is not as serious as it appears. We know of many other organs in which hyperplasia passes insensibly into neoplasia and where hyperplastic and neoplastic lesions may closely resemble one another and may be difficult to separate on purely microscopical grounds, e.g. the breast uterus, liver, thyroid and other ductless glands. In these organs also, neoplasia supervening on hyperplasia is often multicenter. The concept is quite admissible then, that many of the larger nodular masses which develop in a villous synovitis are indeed multiple tumours similar to those that often develop singly in membranes devoid of previous hyperplastic changes. The presence of haemosiderin and lipoid laden phagocytes in some of the solidary tumours is not surprising, for, since hyperplastic masses of synovial tissue are apt to display these secondary changes, neoplastic masses of the same tissue might be expected to display similar changes

A prevalent view that the multinucleated cells in synoxiomas are merely foreign body giant cells calls for correction. True foreign body giant cells may

CHAPTER 44

TUMOURS OF SYNOVIAL TISSUES

INTRODUCTION

Two rather distinct groups of synovial tumours are recognizable

- (a) Moderately common benign predominantly fibroblastic and grant celled growths, most often arising from tendon sheaths and variously designated fibroma endothehoma grant cell tumour myeloid tumour, myeloma xanthoma, benign synovioma or teno synovioma
- (b) Rare malignant growths either of predominantly cystic papillary structure with the synonia filled spaces lined by epith-lium like cells in single or multiple layers or diffusely spindle-celled or pleomorphic celled or often showing both types of structure usually arising from the capsules of larg_joints or from bursae in their neighbourhood and designated malignant synovioma synovial sarcoma or 'sarco mesothelioma'

While most tumours fall readily into one or the other of the two groups, distinction is not absolute some benight tumours (e.g. those described by Black, 1936 and 1940) contain plentiful sprovial mucin and space, lined by epithelium like cells resembling those seen in the malignant group and some of the diffusely cellular sarcomas are clearly the malignant counterparts of the common benigh fibromatous and guant celled growths (see King 1931)

Interpretation of the structure of synovial tumours necessitates clear concepts regarding the structure of normal and hyperplastic synovial membranes once prevalent view that the cells hinng synovial cavities form a continuous pavement endothelium distinct from the underlying connective tissue was The synovial surface is a specialized free connective tissue surface the cells of which are modified connective tissue cells. Modern histologists speak of the lining cells as fibroblasts (Maximow and Bloom 1944 Weatherford 1944) In some places especially in hyperplastic lesions the lining cells are plump and closely aggregated into a pseudo epithelial layer places they are sparse and flattened. The cells on the surface and those just beneath it are not different types of cells, but variants of one type-the synovial and between this and the ordinary collagen producing fibroblast of the surrounding tissue no sharp line of separation can be drawn. Further at chondro synovial junctions there are transitions from cartilage to synovial tissue That synovial cells are only modified fibroblasts is shown also by the transformation of the latter into the former under appropriate conditions, as in false bursae and joints. The close kinship of articular fibrous synovial and cartilaginous tissues explains the structural variations in the tumours of synovial tissues, their varying mixtures of synoviomatous and fibromatous features their angiomatoid characters. and their occasional formation of cartilage or bone as depicted by Buxton

great histogenetic significance. Hence the name "xanthoma" is to be deprecated, for it focuses attention on a purely incidental feature and causes confusion with the lesions of "xanthomatosis" and other phagocytic granulomas to which synoviomas are unrelated. For various reasons, other names are also mapping priate "Endothelionia" is inappropriate for reasons already given "Giant-cell tumour' is unsatisfactory, since some tumours contain few or no giant cells "Myeloid tumour" and "myeloma" are particularly objectionable, for the tumours are quite unrelated to those of bone marrow and bone, and indeed their structure does not resemble that of the giant cell tumour (osteoclastoma) of bone



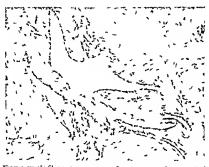
Fig. 336—From a suprapatellar synonoma 3.5 centimetres in diameter from a man of 21 showing lines and cliumps of polyhedral and fusiform tumour cells and densely collagenous partly hyaline matrix. (x 100)

For this reason, as well as for others mentioned by Jaffe et al, Geschicker and Copeland's suggestion, that grint cell tumours of tendon sheaths are osteo clastomas of sesamoid bones, is about

(4) Growth and behaviour

With rare exceptions, the predominantly fibromatous or giant celled tumours of tendon sheaths and other synovial tissues are slowly-growing non invasive being tumours, readily curved by simple enacleation. At the time of their remoral on account of pain or mechanical disability, they have seldom attained diameters of more than 2 or 3 centimetres, but tumours of 5 centimetres or more are recorded. There is usually no difficulty in distinguishing clinically between the common slowly growing circumscribed being synoviomas and the rare, rapidly growing invasive synovial sarcomas. Professor M. J. Stewart has shown me a specimen of undoubtedly malignant synovioma of giant celled type, which invaded neighbouring soft tissues.

possibly occur in some of the turnours in which lipoid phagocytes abound but as Stewart and Flint insisted, most of the giant cells are undoubtedly tumour cells. Their nuclei which are identical in appearance with those of the surrounding mononucleated turnour cells are scattered throughout their cytoplasm. They rarely contain lipoids but they often contain haemosiderin. These large cells have all the appearance of being syncytial aggregates of the smaller turnour cells and not primarily phagocytic at all. Since however, the turnour cells are of mesenchymal type it is not surprising that they themsleves should take up extravasated pigments. The haemosiderosis of the cells does not mean that they are merely scavengers.



Fio. 335 — From a mainly fibromatous synovious 2 centimetres in diameter attached to flevor tendon sheath of thumb of a man of 33 years—showing synovial clefts with villous projections in the tumour (× 100)

(3) Structure, histogenesis and nomenelature

The tumours arise from and consist of synovial tissue and are therefore appropriately named synovionas Sub-division of the group into fibrous mucinous vascular giant-celled cartilaginous osseous lipomatous and mixed types is unnecessary and impracticable for many tumours are mixed showing combinations of the different structural variants. The commonest of these are led and fibrous which are often seen in combination and in which "felts are often present (see Figs. 335-336). The tumours

tress in which polyhedral spindle shaped or us matrix these areas often alternate

areas Primarily, many of the solitary the or no extravasated blood pigment or the brances and the phagocytic activity

rominent are secondary and of no

Case I—History—For 18 months a man of 71 had an enlarging mass on the inner aspect of his knee joint of peration showed this to be a well defined hemispherical timour 14 centimetres in diameter attached to the external surface of the capsule of the joint by a pedicle 4 centimeters in diameter. A disc of the capsule was removed along with the tumour which weighed 540 grammes. On section it was found to consist of a fine honeycomb of spaces filled by mucinous material. Microsopically (Fig. 338) these were lined by layers of cells of variable appearance and thickness in som places resembling an epithetial reticulum in others to ensisting of strands of elongated cells traversing mucinous material, and in others resembling myxoms.

(1) Age, sex and site incidence

Knox s and Fisher's reviews show that malignant tumours of synovial membranes occur with about equal frequency in men and women. They may

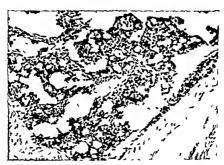


Fig. 338—Case I Malignant synovioms of pseudo-epithelial type showing a tumour meshwork with mucus filled spaces (x 120)

appear at any age after childhood, the greatest numbers of patients being in the third and fourth decades. In about one half of the cases the growths arise in the region of the knee either from the capsule of the knee-joint itself of from neighbouring bursae, especially on the popliteal aspect. The other principal sites of origin are the ankle region and foot, forearm wrist, elbow and thigh Very few of the tumours have commenced in the hands (the commonest site of beingn synoviomas) toes, shoulder grdle, or in the joints of the head, neck and trunk. Most of the tumours arising from joint capsules project externally from the capsule and often do not invide the joint cavity. This suggests that their origin is less often from the lining of the joint itself than from synovial cysts in the capsule of the knee joint, where such cysts are common. However, there is no evidence that the common synovial ganglia of the wrist region are predisposed to tumour formation.

MALIGNANT SYNOVIOMAS OR SYNOVIAL SARCOMAS

Malignant tumours of synovial origin are either (a) solid anaplastic spindle celled or pleomorphic celled sarcomas in which synovial differentiation is lacking or indefinite or (b) cystic or papillary growths of pseudo epithelial structure often containing gelatinous synovial secretion. These two types are probably

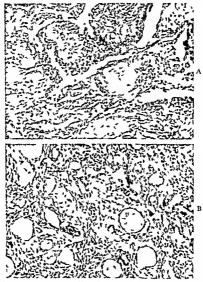


Fig. 337 — Malignant teno synovioma of foot of pseudo-epithelial () pe A = papillary structure B = pseudo acutar structure $\{x | 150\}$

not distinct but represent merely the more or less anaplastic tumours of the one kind. Those of type (a) exemplified by my necropsy Case No. 218 (Willis 1934) are rarer than those of type (b). Good accounts include those of Prym. Knox Hutchison and Kling Briggs and Fisher. I have examined two specimens of the cystic mucinous type of growth, one of these depicted in Fig. 337 arose in the sheath of one of the flexor tendons of the foot in a man of 51 years, and the following are brief notes of the other.

CHAPTER 45

ANGIOMAS TUMOURS AND TUMOUR-LIKE OVERGROWTHS OF VASCULAR TISSUE

INTRODUCTION

SEVERAL factors complicate the discussion of tumours of blood vessels and lymph vessels. In the first place, most so called 'angiomas' are not true tumours but vascular malformations or 'hamartomas', while some others are vascular masses of reparative tissue. But, in the second place, distinction between the true neoplasms and the hamartomas of vascular tissue is not always easy, for in the latter seemingly infiltrative structure and multicentric formation may readily simulate invasive growth and metastasis. Thirdly, many malignant tumours of other kinds have been wrongly identified as angiomatous merely because of their great vascularity. Fourthly, since the potencies of proliferating mesenchymal tissues are very diverse, sharp separation of angiomas from other mesenchymal growths is to some extent arbitrary. Before going on to consider angiomas as neoplasms, let us consider these four confusing factors more fully

(1) Most "angiomas" not true tumours

Most pathologists will concur in this proposition. Briefly, the grounds for it are as follow

- (a) Many "angiomas" are congenital. Those of the skin, which are the commonest form of 'brithmarks', are obvious at birth or are noticed soon afterwards (see Figs. 339-343). Fitzwilliams found that 83 per cent of vascular naevi of the skin were noticed at birth, and an additional 13 per cent within 6 months. Those of the deeper tissues may not be discovered until later in life, but these also, when they involve functionally important parts such as the nervous system usually give evidence of their presence during childhood or early adulthood. Parkes Weber speaks of naevi as 'developmental—mostly congenital—dysplasias'.
- (b) No structural distriction is possible between "angiomas" and acknow ledged vascular malformations such as pleutform or serpentine angiomatosor mere supernumerary vessels. Indeed the structure of many "angiomas shows clearly that they are masses of tangled or deformed supernumerary vessels—capillaries, veins, arteries, or all three. The larger vessels often have well developed muscle coats or irregular masses of muscle fibres in their walls (see Fig. 340, and Case I below).
- (c) Above all, the common vascular hamartomas have no powers of progressive disproportionate growth. Like any other malformation, the birthmark grows along with the issues of which it is a blemish, then, unless accidents occur in it usually ceases to increase. Accidents which may cause its enlargement, namely, haemorrhages, cystic changes inflammation, thrombosis and oedema, may give it a false clinical appearance of neoplastic growth, and in certain situations,

(2) Structure

The two main varieties of structure found alone or together, in synovial sarcomas are

(a) Cystic and papillary formations with synoxial fluid in the spaces

The spaces are often bined by a compact layer of polyhedral tumour cells one or several layers thick giving a pseudo epithelial appearance superficially resembling that of disorderly papillary adenocarcinoma (Figs 337 338) Closer examination however usually reveals the non-epithelial character of the cell layers these possess no proper basal border, but merge with the diffusely arranged surrounding cells. The relative amounts of pseudo-epithelium and intervening diffusely cellular tissue vary widely sometimes as in the specimen of Fig. 338 the bulk of the tissue forms pseudo carcinomatous structures, in other tumours the bulk is diffusely sarcomatous with only occasional clefts lined by compact cell lavers

(b) Diffusely cellular sarcoma

This consists of either spindle cells polyhedral cells or pleomorphic cells Indefinite enithelium like clumps may be found in parts and myxomatous areas also occur

(3) Behaviour

Only occasional tumours of this kind appear to have been cured by excision or amoutation. In most cases recurrence or metastasis has developed. The lungs are the main site of metastases and these may appear several years after removal of the primary growth e.g. 4 years in Knox's third ease. Metastases in the regional lymph glands as in my necropsy case referred to above are unusual In structure the metastases may reproduce the distinctive synomial characters of the primary growth as in Fisher's first case or they may be more anaplastic. as in my case

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an already existing malformation Thrombosis, organization and fibrosis some times lead to reduction in size of "angiomas"

(d) Some acquired 'angiomas" are not malformations but masses of vascular reparative tissue or cetatic vessels. Thus, Mailer advanced good reasons for believing that some of the so called "angiomas" of skeletal muscle are post traumatic masses of granulation tissue under peculiar mechanical conditions, and there is little doubt that not a few of the acquired "angiomas" of skin and nucous membranes are merely masses of inflammatory tissue—inflammatory granulomas"—the products of delayed or thwarted healing. Many acquired telangicetases, such as those of the face of plethoric elderly people, are of course

due merely to local dilatation of vessels from obstructive or degenerative causes
Before assuming, then, that any given mass of highly vascular tissue is a truly
neoplastic angioma, the question should be asked can this be either a vascular
malformation, altered maybe by supervening accidental changes, or an extravagant
mass of post-traumatic or post inflammatory reparative tissue, or merely a
varicosity of ectasia? The answer will usually be in the affirmative

(2) Distinction between vascular hamartomas and neoplasms sometimes difficult

Vascular hamartomas, by their very nature, are usually poorly demarcated and show intimate mingling of the superfluous vessels with the normal tissues of the part. This may give a false appearance of invasive infiltration, and, especially if the hamartoma consists of fine capillary vessels or of more cellular areas of non canalized vasoformative tissue, its microscopical appearance may closely simulate that of an invasive growth. If also, as is not uncommon multiple hamartomas of this kind are present in several tissues, say in the spleen and liver or in the liver and lungs then these multiple foci may simulate metastases. In 1934 I reviewed and discussed many examples of this kind to which may be added the case described by Taylor and Moore. While in many of these case especially in infants, it is clear that multicentric growth accounts better for the findings than metastasis, in some others in adults it is difficult to teach a confident decision, and the possibility of the growths being metastasizing angio sarcomas must be admitted (see below).

(3) Vascular tumours of other kinds wrongly diagnosed as "angiomas'

No modern pathologist should be so misled by finding blood within adeno carcinomatous spaces that he mistakes renal or other carcinomas for "haemango endotheliomas", as was once done let as Stout properly points out, the last edition of Ewing's text-book (1940) contains an illustration (Fig. 133) labelled "angio endothelioma of bone" which almost certainly perpetuates this old error, and Thomas (1942) has made a similar mistake

More excusable, but still unfortunate, is the tendency to assume that diffusely cellular highly vascular growths of uncertain nature are angioblastic. This assumption has led to many errors of diagnosis. Anaplastic growths both carcinomas and sarcomas may contain abundant vessels closely invested by the tumour cells a way falsely suggesting special angioblastic properties of the tumours. The stion arises what degree of vascularity, what ratio of vascular channels to have reasonable accordance of the tumour cells are reasonable to the control of the tumour of the tumour cells are reasonable to the control of the tumour of the tumour cells are reasonable to the tumour of tumour of tumour of the tumour of tumour

e g in the brain, such enlargement may make it as dangerous as any tumour and necessitate its removal. Even when an angioma appears to extend its territory



Fig. 339—Angioma of dermis of shoulder present since birth excised when child was 12 months old (× 120)



Fig. 340—F om a plaque like angroma of skin of shoulder 5 centimetres in diameter excised when child was 14 morths old showing a capillary plexus and part of wall of a large arterial vessel (× 150)

without having suffered any such accidents this is probably due, not to proliferative growth but to canalization and establishment of a blood flow in fresh parts of

(1) Haemangiomas of particular tissues

(a) The skin and subcutis

The familiar "angiomas" or vascular naevi of the skin— "De Morgan or ruby spots, 'spider naevi', "mulberry naevi", 'port-wine stains', etc—are adequately described in many text books, have recently been well summanized by Harvey et al and by Weber, and call for no special description here. Their structuril variants, described as capillary, cavernous and plexiform, are often seen in combination, and the lesion often extends also into the succitaneous



Fig. 341—From a pedul_{in}culated birthmark i centimetre in diameter, of skin of neck ercised from a woman aged 30 showing patent capillary channels and patches of incompletely canalized vasoformative tissue \ (x 150)

tissues and occasionally into the underlying muscles or bones. A type of structure particularly noteworthy because it may simulate that of a cellular neoplasm, is the poorly canalized capillary type with tangled masses of closely aggregated vasoformative cells and but few patent vascular channels (Fig. 341). Canalization of such tissue probably, accounts for the seeming extension of some angiomas. The following case exemplified the great variety of structure seen in angiomas.

Case I—Male 2 \ History—Buthmark of skin of salf present since both with mo change until recently, when it became painful was excised. It was a cutaneous and subcutaneous angioma 41 centimetres in dameter from which some thrombosed wene passed through the deep fast in into the muscle. Histology—Growth was a mixture of vascular channels of great differently including canalized and non-canalized capital is large cavernous spaces welly formed arteries and many large versels with irregular luminary and thick missular walls in which bundles of smooth muscle fibers rain in various directions. Many large patches of Winsiele contained relatively few asscular channels. Many normal cutaneous glands and net rees were submerged in the vascular growth. Some of the nerves contained angiomatous of seeks [Fig. 32].

question difficult to answer. On the one hand I am satisfied that great vascularity has often led to a false diagnosis of malignant angiona and on the other hand I have seen several tumours in which a highly vascular pattern appeared to be a distinctive and widespread feature strongly suggestive of a special angioblastic habit of growth. Reasonable confidence regarding the angiomatous character of such a tumour is however to be attained only by a most thorough examination of all parts of it and in many cases by necropsy study to ensure that the growth in question is indeed primary and not a peculiar metastasis of some unsuspected primary tumour elsewhere.

It is to be recalled here that highly haemorrhagic characters are not peculiar to angiomatous growths but are seen also in chonon epithelioma and in anaplastic carcinomas and sarcomas. Ogilive and Mackenzie reported two tumours as 'malignant haemangio endotheliomas and later with commendable frank ness retracted this diagnosis in one case and identified the growth as chorion epithelioma.

(4) The diverse potencies of mesenchymal tissues

It was pointed out in Chapter 41 that the ready metaplastic conversion of proliferating mesenchymal tissue of one kind into itssue of another kind seen in both non neoplastic and neoplastic lesions makes the grouping of mesenchymal tumours into separate species somewhat arbitrary. Since fibromas sometimes ossify chondrify or undergo mucoid change why should they not sometimes undergo predominant vascular differentiation as they grow? Such a conversion indeed happens with the meningiomas—some of these are so abundantly vascular that they have been called angioblastic meningiomas. (Wolf and Cowen Bailey and Bucy) and all gradations are seen between structurally typical meningiomas and predominantly angiomatoid growths. Evidently then pre-dominantly angiomated structure in a mesenchymal tumour does not necessarily denote a specific vascular origin. Every actively growing tissue is bound to have an adequite blood supply and actively growing mesenchymal tumours marticular may well develop their vascular changes to an extravagant degree for their tissue is of the very lineage that makes blood vessels. Let us be cautious then, not to pronounce highly vascular mesenchymal growths 'angiomatous', save on very secure grounds.

A BRIEF SURVEY OF ANGIOMATOID MALFORMATIONS

Because most so called benign angiomas are not neoplasms but malformations this book is not primarily concerned with them. However some knowledge of their distribution and structure is necessary to a critical consideration of tumours believed to be truly angiomatous. Hence a brief survey of them is given here under the following main heads

Haemangiomas of particular tissues Multiple hiemangiomatous syndromes Lymphangiomas 706 ANGIOMAS

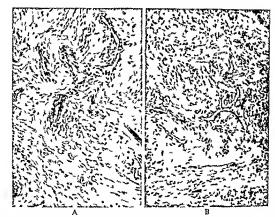


Fig. 343—Case II Congenital angioma of muscle, showing muscle fibres separated by mesen chymal tissue with many blood vessels B—includes also many leucocytes (× 120)

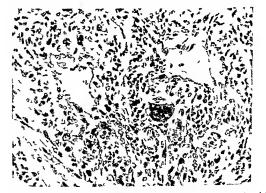


Fig. 344—Case II Details of vascular spaces intervening mesenchyme and a multimucleated giant cell (× 300)

(b) Skeletal muscles

Angiomas of muscles have been described and reviewed by Jenkins and Delaney, Mailer and MacDermott In over 80 per cent of reported cases the patients have been under 30 years of age many of them children. The muscles most often affected are those of the thigh and calf the biceps and triceps of the arm, latissimus dorsi and masseter. Besides the developmental origin suggested by the age incidence, trauma may produce angiomatoid lesions in muscle as suggested by Mailer, or possibly enlargement of a developmental lesion as the result of injury, haemorrhage and thrombosis may bring it to clinical notice or



Fig. 342—Case I. A nerve bundle surrounded by and containing cavernous vascular channels (\times 150)

may simulate neoplastic growth. The following two examples of angiomas of muscles are worthy of note

Care II—At birth a male infant was noticed to have a bulky swelling of its rectar femoris. Exploratory operation disclosed a very vascular growth diffusely involving the distal two-birds of the muscle. A piece removed for microscopical study showed the bundles of muscle fibres separated by richly vascular meschehymal tissue including many explicative seeds and small venis many flump pervisual rushed and stellate cells scattered collections of lymphocytes and other leucocytes and some large triegular multi-nucleated cells resembling megakarjocytes (Figs. 34). 34). The appearance was thus that of a highly vascular young mescachymal tissue with some harmoponeus also in progress.

Case III—I or 5 years a woman aged 21 had noticed a rounded mass near the stemum this was excised and found to be an ill-defined vascular growth 2 contineties in dameter in the pectoral muscle. Handays—Typical beings cavernous angioma triingled with muscle fibres—the walls of the vascular spaces contained plentful smooth muscle.

sub division clinically convenient, it is not warranted pathologically. With rare and doubtful exceptions, all angiomas of the nervous system are developmental vascular hamartomas, and all gradations between and combinations of the several structural types occur. The variability in structure and distribution of the lesions is well shown in Wolf and Brock's series. The cerebellar growths show as little structural evidence of neoplastic qualities as other "angiomas", attribution of such qualities to them by clinicians has been merely because they are space occupying lesions in a region where any chargement—from cystic changes or vascular accidents—is certain to cause dangerous results.

Weiss described a cerebral eavernous angioma which contained also bone and glial tissue Bailey and Ford pointed out that angiomas of the nervous system, like those of other regions, may show selerosing, pigmentary and lipoid changes, and that both neuroglia and connective tissue may participate in the selerosis. An interesting and frequent feature of angiomas of the brain is the presence in or around them of many small degenerated vessels which have become converted into calcified cylinders (Urban, Zeldenrust, Turner). Sudden fatal haemorrhage from angiomas is not unusual, as in Turner's case and the following case.

Cose IV —Female 35 Sudden onset of rapidly fatal coma cerebrospinal fluid blood stained Necropy —Spongy haemorrhagie area 3 centimeters in diameter in antenor part of right internal capsule all other organs normal Histology —Typical cavernous angioma with recent thrombosis and haemorrhage periphery shows many small calcified tessels

Other anomalies of the nervous system may be associated with angiomas, e.g. syringomyclia (Russell, Wolf and Wilcins). In Wolf and Brock's second case an arterio venous angioma of the frontal lobe was continuous through a deficiency of the bone with an angiomatous mass beneath the skin. Associations with cutaneous or visceral angiomas or other anomalies are described later.

(e) Peripheral nerves

Nerves are rarely the site of angiomas Purcell and Gurdian saw a caver nous angioma of the sciatic nerve in an infant, and referred to occasional earlier records Bergstrand described an angioma of the tibial nerve in a man aged 31 but his contention that this was malignant and had metastasized to the lungs cannot be accepted, the lung tumours were of quite different structure

(f) Viscera

The well-known cavernous angiomas of the *liner* need no description here, noteworthy bowever, is their loss of vascularity and conversion into fibroma like areas, as described by Merkel Multiple or diffuse angiomatosis of the liver is occasionally seen in infants, sometimes with and sometimes without similar lesions in the spleen, lungs skin or other parts (Falkowski, Foot, Orzechowski, Taylor and Moore, and see Fig. 346) Small cavernous angiomas of the spleen are not rare, they are prone to cystic changes and nitra cystic haemorrhages and I think it likely that most non epithelial splenic cysts arise in this way Angiomas of the *intestine* have been reported by Merchant and by Lockhart Mummery, of the *kidney* by Swin and Balme, of the *adrenal* by Menon and

(c) Bones

Haemangiomas of bones were carefully studied by Bucy and Capp who found that these lesions were nearly all of the evernous type that their most frequent sites were the vertebrae and skull and that radiographically they produced rather distinctive appearances. In flat bones like the skull scapula and pelvis, a promunent sun burst appearance due to new formed bone trabeculate radiating from the surface of the bone is usual, in vertebrae, prominent vertical trabeculation and in tubular bones loculated expansive lesions. Other noteworthy papers are those of Makrycostas Scherer Karshner et al and Pulveritit on vertebral angiomas, and of Anspach Pich and Kaplan and Kanzer on the sunray 'angiomas of the skull. The latter have often been misdingnosed 'sarcoma' from their radiographic appearances but they are benign lesions

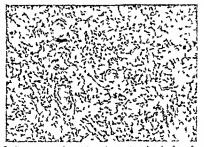


Fig. 345—Capillary angioma of cerebellum showing a meshwork of vasoformative tissue largely non-canalized traversed by some larger vessels which have undergone thrombosis (x 120)

which as in Anspach's case may remain stationary for many years. A peculiar tumour of a child's skull possibly related to the sunray angiomas is described as Case I Chapter 43.

(d) Central nervous system

In their monograph in 1928 Cushing and Bailey divided vascular growths of the brain into two main groups—angiomatous malformations and haeman gioblastomas or true tumours. The former include capillary cavernous venous and arterial malformations comparable with those of the skin. The commonest of the haemangioblastomas are those occurring in the cerebellium in young adults the tumour consists of a mass of tangled small vessels or vasoformative tissue either solid or cystic (Fig. 345) often with only a relatively small nodule or plaque of growth in the wall of a large cyst (Urban. Cox and Trumble) Capillary angiomas of the cerebrum are rare (Barnard and Walshe)

Although many subsequent workers have found Cushing and Bailey's

(c) Coexisting multiple angionios of skin and encliondromas of bones (Olher s disease)

This rare association, "Kast's syndrome", has been reviewed by Carleton and Robb-Smith and by Carleton et al, who described a woman aged 32 with multiple enchondromas of the hands and multiple haemangiomas of the skin and subcutaneous tissues and of several bones. Of the few recorded cases, most have been males

(d) Coexisting angionias of skin and central nervous system or its coverings

(See Cushing (1906), Cobb, Rogers, Peters and Tebelis, Cox and Trumble, Karshner et al., Nussey and Miller) In these cases the presence of vascular naevi on the face or elsewhere points to the nature of the central nervous lesion. The nervous and cutaneous lesions often affect the same segmental level, eg facial naevi accompany cerebral lesions, and the level of trunk naevi corresponds to that of the growths affecting the spinal cord. Specially associated with the names of Sturge, Weber and Kalischer is a group of cases showing facial and leptomeningeal naevi, aecompanied by radiographically visible calcification of the brain, and often by epilepsy, mental retardation and glaucoma. In Wolf and Brock's third case, a facial naevis coexisted with extensive venous angiomatosis of the retina, optic nerve, eavernous sinus, base of cerebrum, brain stem and cerebellum.

(e) Coexisting angionias of retina and central nervous system and visceral abnormalities

(See Lindau, Collier, Davison et al) The complete syndrome, often called Lindau's or von Hippel-Lindau's disease, comprises angiomatosis of the retina angiomas of the certeal nervous system usually of the cerebellum, and vanous visceral lesions including cysts of the pancreas or kidnev and renal adenoma In some instances, as in Collier's cases, angiomas of the brain coexist with visceral lesions but retinal angiomas are absent. The case described by Wolf and Wilens showed a cystic angioma of the crebellum, three small angiom of the spinal cord, syringobulbia and syringomyclia, cysts of pancreas and kidneys, adenoma of the kidney aberrant adrenal tissue in a retroperitoneal lymph gland and three chromaffin tumours of the left adrenal gland. Lindau's disease is familial in about 20 per cent of cases, some members of a family may have retinal lesions, some brain lesions and some the complete syndrome

(3) Lymphangiomas

"Cyste hygroma" of the neck or axilla has excited the interest of pathologists since Wernher's account (cited by Goetsch) in 1843. Treves described a huge hygroma which extended from the floor of the mouth to the lower rib margin in an infant 3 weeks old. Goetsch's paper contains an admirable review of the subject and a detailed study of 12 cases.

(a) Site

The favourite sites of lymphangiomas are the neck and axilla, but they occur also in the arm, mediastinum, mouth region and abdomen Perlmann

Annamalai of the omentum by Stout and Cassel, of the placenta by Strachan and by Marchetti

(2) Multiple haemangiomatous syndromes

Vascular hamartomas in a single tissue such as the skin or central nervous system are often multiple, e.g. in 16 per cent of patients with angiomas of the skin (Fitzwilliams). But two or more different tissues such as the skin and nervous system or the spleen and liver may be affected simultaneously. Eponym enthu siasts have made the most of the many possible combinations of sites and combinations of angiomas with other abnormalities. Here it must suffice to give only brief notes and references to the more important syndromes and to refer to Weber's useful outline.

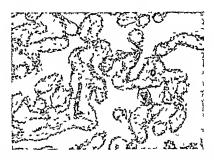


Fig. 346—From a specimen of diffuse extensive angiomatosis of liver of a new born infant. Note the inclusion of bile ducts in the sepia between the vascular spaces. (× 120)

(a) Hereditary multiple telangrectasis of skin and mucous membranes

(See Osler, Goldstein MeArthur Schuster and Cappon.) Multiple punctate modular or spider naevi develop on skin and visceral linings usually during childhood or adolescence persist throughout life and cause recurring haem orthages from mucous membranes. The disease is familial affects and is transmitted by both seves and behaves as a Mendelian dominant. Schuster saw coevisting multiple ancurysms of the splenie artery and venous anomalies in lungs and liver

(b) Coexisting angiomas of skin and viscera

These may affect various organs eg skin liver and spleen (Falkowski) skin liver and lung (Orzechowski Taylor and Moore) skin lungs thyroid intestines, etc (Jaffo, skin stomach intestines, lutey and adrenal (Merehant)

lined by epithelium, which has been flattened and disguised in most situations by obstructive distension of the cavities. The presence of lax non distended or ramifying spaces also lined by flat non epithelial cells will usually make the nature of the lesion clear. Microscopical distinction between epithelial and lymphatic cystic growths may sometimes be impossible. Supposedly lymph vascular lesions of even non epithelial organs are sometimes epithelial, thus the "lymphangio endothelioma" of the heart reported by Perry and Rogers was almost certainly an opithelial heterotopia similar to those described by Davidsohn and Rezek

(b) Sex and age

The sexes are nearly equally affected females slightly predominating. Most of the cervical and axillary growths are noticed at birth, but some do not appear until later. Some internal tumours announce themselves early, e.g. in Case V above but many of them are not discovered until adult life, and many of those discovered late show dense fibrous walls and septa and other signs of long duration and quiescence.

(c) Structure and growth

Goetsch gives a full account with many good figures, and interprets the growth of hygroma as follows "Endothelial fibrillar membranes or sprouts from the walls of the marginal cysts penetrate the adjacent normal tissues. A lymph-like fluid is secreted within the fibrillar, which are thereby caused to spread apart and canalize. Minute cysts with an endothelial lining are thus formed within these sprouts. By continued secretion within, the cysts enlarge, by pressure atrophy of the walls between adjoining cysts, the large cavities character istic of hygroma are formed." The extending cystic lesion mingles with or invests neighbouring nerves, muscles or other structures. Goetsch points out how this mode of growth resembles that of the developing lymphatic system.

Other noteworthy features in the hygromas of the neck and axilla which I have studied have been (i) the abundance of irregularly distributed smooth muscle in the walls of many of the larger channels, similar to that seen in haemangiomas (e.g. Cases I and III above), (ii) the frequent presence of patches of lymphod tissue as an integral part of the growths, and (iii) the frequent presence of many large or irregular blood vissels mingled with the lymphatic spaces suggesting that haemangiomas and lymphangiomas may not be sharply separable but that

lesions of mixed structure occur

(d) Malformation or neoplasm?

Goyetsch believed that the mode of extension which he described shows hygoma to be an true infiltrating neoplasm and not merely an enlarging cystic malformation. In my oppinion, however, fluid accumulation the progressive formation of collateral channels in and in some cases supervening thrombosis and organization, suffice to account for the growth of hygomas. The mingling of the lymphatic channels and cysts with the envolved tissue is not a proliferative invasive process, but merely a necessity feature of a vascular malformation comparable with that seen in haemangiomas. It Like haemangiomas, lymphangiomas are often known to be

reported a lymphangoma in the Aidney and Rabson and Zimmerman one in the adrenal, and I have seen the following examples in the mesentery pancreas, kidney and epididymis

Case V—Female aged 4 years and 8 months Recent abdominal pain laparotomy—rounded lobulated tumour 12 centimetres in diameter situated in mesentery closely contiguous with bowel a loop of which had to be removed with tumour This consists of honeycomb of large and small cysts with watery fluid Histology—Cysts devoid of epithelium and lined by flat cells fibrous septa contain similar small ramifying ciefts

Case VI—Female aged 67 Abdomnal mass noticed for 3 years not enlarging Removal of kidney with well defined tumour 15 centimetres in diameter replacing a small part of centre of organ and projecting laterally from it. This shows a honeycomb of large and small cysts separated by fibrous septa and containing watery fluid. Histology—Cysts everywhere lined by flat non-epithelial cells.

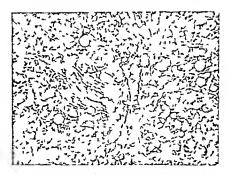


Fig. 347 -Case IIII Lymphangioma of epididymis (x 120)

Care VII — Female aged 87 Incidental necropsy finding a well-defined honeycomb cystic mass 8 centimetres in diameter in head of pancreas microscopically similar to that in previous case

Case VIII—Well-defined firm white growth 2 centimetres in diameter was excised from epididymis of elderly man who had noticed it slowly enlarging for 2 years. Ilistology (Fig. 347)—Tumour consists of a honeycomb of rounded or elongated spaces 10 to 40 µ in diameter lined by large flat polygonal cells and separated by a variable amount of dense fibrous tissue. The spaces appear empty containing no blood corpuscles or obvious secretion (Compare with specimens depicted as epididy momata by Baillie).

Needless to say great caution is needed before diagnosing as lymphangiomatous a cystic growth in an epithelial organ very thorough microscopical study of many parts must be undertaken in order to exclude the possibility of the cysts being

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The following is a typical example

Case IX—Male, aged 22 Pamful purplish red dome shaped mass 1.5 centimetres in diameter present for many years on anterior aspect of middle third of right shine exession of mass which involved only skin and subcutaneous tissue. Histology (Fig. 348)—Many



Fig. 348—Case IX Glomangioma A = large and small vascular channels with zones of glomus cells in their walls B = a large mass of glomus cells (\times 100)

well formed large vascular channels contained plentiful closely packed polyhedral cells in their walls arranged either in even strata separated from the lumina by a layer of intima or in large irregularly distributed masses between the vessels

present at birth, and many of those not discovered until adult life as in Cases VI VII and VIII, show clear structural evidence of old age and quiescence

TRUE ANGIOBLASTIC NEOPLASMS

We come now to the difficult question do truly neoplastic angiomatous growths occur? I have seen no evidence to lead me to alter the opinions reached in my 1934 work, which were briefly that, while malignant angioblastic growths probably do occur and sometimes produce blood borne metastases they are very rare and most supposed examples are either multifocal hamartomas or vascular tumours of other kinds Additional to the cases reviewed in 1934, those subsequently described by Robinson and Castleman and by Stout support the view that genuine angioblastomas or at least mesenchymal tumours with predominant vasoformative qualities do occur. I am less satisfied regarding the tumours reported by Hall Ogilvie and Mackenzie (second ca.e) and Murray and Stout which may have been only vascular sareomas of other kinds. In Hewer and Kemp's case of haemangio endothehoma of the heart, the supposedly metastatie tumours in the lungs and elsewhere may well have been like the cavernous angiomas of the oesophagus and liver which were present, benign multifocal lesions. The angioblastoma of the spleen with metastases in the described by De Navasquez resembled those of Jores Wright and others which as suggested in my 1934 work may be interpreted as multifocal ' system lesions rather than as metastasizing neoplasms. However that metastasis may be the correct interpretation of these cases cannot be excluded

The conclusion that true tumours of vasoformative tissue indeed exist does not imply that these are to be distinguished sharply from other mesenchymal tumours Let us recall once again the intermutability of the various mesenchymal tissues the close kinship of their tumours and the fact that vascular tissue is of all the mesenchymal tissues the most ubiquitous and one of the most plastic Then we will be prepared to regard true angiomas and angiosarcomas not as fixed species but merely as conspicuously vasoformative variants of the genus mesenchymoma

ANGIOMAS AND ANGIOMATOID HAMARTOMAS IN ANIMALS

Feldman (Chapter XI) gives references to many haemangiomas and a few lymphangiomas in horses, cattle and dogs rarely in other species. Nieberle and Cohrs refer to or depict multiple cavernous angiomas of the lung of the ox of the intestine of the horse of the liver in the ox horse sheep cat dog and fowl and of the bladder in the horse. As in man, so in animals, probably most angiomas are hamartomas rather than true tumours but true neoplasia and metastasis certainly occur Rudduck and I examined 2 cavernous aneiomas of the skin in fox terriers an angiosarcoma of the wing of the atlas with metastases in the lungs in a greyhound an angiosarcoma of the buttock in a Scottie, and diffuse angiomatosis of the liver in a male chinchilla cat aged 3 years

GLOMANGIOMA

For detailed accounts and reviews of this tumour see Masson Mackey and Lendrum Freudenthal et al Stout Lendrum and Mackey, and Murray and Stout

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(1) Origin and site

Masson s discovery of the neuro myo arterial glomera of the skin and sub cutaneous tissues and his demonstration of these as the source of the tumours now called glomangiomas have been fully confirmed by later workers. The normal glomus is now recognized as a convoluted arteriolar venous anastomosis with a characteristic cellular wall containing a thick layer of cubodal epithelium like cells. Murray and Stout have advanced strong evidence that these epitheliod cells are identical with the capillary pericytes of Zimmermann which are akin to the muscle cells of arterioles. The tumours are usually small and well defined rarely more than 2 or 3 centimetres in diameter usually single but sometimes multiple. They have occurred in adults of all ages but only rarely in children Harvey et al depict a glomangioma present since inflancy in a girl aged 7. Glomera have been demonstrated most abundantly in the integuments of the penipheral parts of the limbs and these are the commonest sites also of the glomus tumours. The undoubted occurrence of similar tumours of the penis trunk face and more rarely of muscles and other deeper tissues, shows that glomera are of wider distribution than was at first supnosed.

(2) Structure

The growth consists of cavernous vascular spaces the walls of which contain even layers or irregular masses of the characteristic glomus cells. These are uniform in size polyhedral have central rounded darkly staining nucle 7-10 \(\mu\$ in diameter and are usually separated by distinct cell walls. Transitions from cuboidal glomus cells to spindle cells indistinguishable from smooth muscle fibres are sometimes to be seen a point which accords with the view that glomus cells are identical with Zimmermann's pericytes. Glomangiomas may include extensive masses of glomus cells traversed by only scanty vascular channels. or, on the other hand they may show predominant vascular structure with only scanty cuboidal cells in the walls of cavernous spaces. Between the vascular spaces lie varying amounts of connective tissue with or without smooth muscle fibres and nerves are often to be seen at the periphery or in the septa of the tumours.

(3) Growth and behaviour

Glomangomas constitute one variety of the group of lesions formerly designated painful subcutaneous tubercle which included also painful leio myomas neurofibromas and inflammatory nodules. Because of the severe paroxysmal pain which often attends them especially when situated on the limba, glomangiomas are usually removed while still quite small. They are usually well-circumscribed slowly enlarging benign lesions, but Murray and Stout reported an infiltrating recurrent growth of this kind. Excision of the growth abolishes the attacks of print.

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Case II - (Mr H C Trumble 5 case) A woman aged 50 had noticed unilateral exophthaimos and swelling in temporal fossa for many months. Skiagrams showed great thickening of temporal bone lesser wing of sphenoid etc. Operation disclosed flat plaque like growth forming velvely layer up to 4 millimetres thick on inner surface of dura over an pregular area of 4 centimetres in main extent with multiple natches of growth in the area the dura was stripped and part of the bone removed Histology (Fig. 350)-Typical moderately cellular whorled meningioma invading dura and bone

(2) Microscopic structure

Like other kinds of mesenchymal tumours, the meningiomas show wide variations of cytology and pattern, and sometimes develop bone or other



Fig. 351 - Epithelioid structure in para sagittal meningioma 7 centimetres in diameter from a boy aged 15 (x 150)

kinds of heterotopic tissue Bailev and Bucy proposed to distinguish 9 types of growth-mesenchymal, angioblastic, meningotheliomatous, psammomatous osteoblastic, etc However, these are not distinct types but merely variants of the single entity meningioma. The variability of cell form and growth pattern of meningeal tissue in culture, revealed by Cox and Cranage s and by Bland and Russell's studies, accords with the structural gradations and combinations seen in the tumours These are is follow (Figs 351-356)

(a) Epithelioid form

Closely packed plump polyhedtal or clongated cells form well defined epithelium like clumps, often with a whorled arrangement of the cells, set in a vascular connective tissue stroma

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(c) Psammoma form

More or less plentiful calcified spherules are scattered through growths of the preceding forms Many of these spherules occupy the centres of whork,

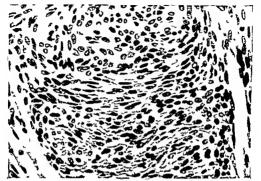
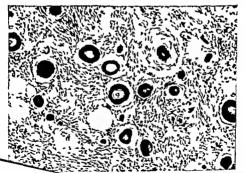


Fig 354 - Detail of Fig 353 (× 400)



hingioma with calcified spherules from thoracic part of the spinal (× 120)

them or in non-whorled areas, they often show regular Calcification commences both within tumour cells and olid centres of whorls, and only occasionally in the walls

(b) Whorled spindle celled form

Plump spindle cells are arranged in contiguous whorls which however are not sharply circumscribed but coalesce at their margins. The whorls range from

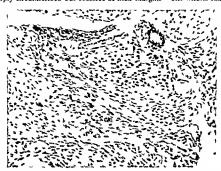


Fig. 352 —Epithelioid structure with small whorls in a meningioma from a man aged 40 (x 150)

20\(\mu\) to 100\(\mu\) or more in diameter. They sometimes contain small central blood vessels but are much more often solid throughout. Collagen fibres are sparsely



Fig. 353 -- Whorled but non-calcified m-ningioma (x 90)

mingled with the whorled tumour cells but the central parts of whorls often undergo conversion into livaline spherules of collaren

(g) Sarcomatous form

Diffusely cellular growths, devoid of calcification and with only slight or no signs of whorling, are not rare. When these signs are completely lacking it is

impossible to be sure of the meningiomatous nature of the tumour

Again it must be stressed that the foregoing are not distinct kinds of growths but merely structural variants, combinations or transitional structures are often seen in one tumour, particularly the forms (a) to (e) Other occasional structural features are aggregations of lymphoid cells or of lipoid foam cells

GROWTH AND BEHAVIOUR

(1) Rate of growth

The rate of growth varies greatly Some patients have symptoms for many years before operation, or long periods elapse between removal of the tumour and recurrence, in other cases the symptoms are of brief duration and rapidly progressive, or promptly recurrent growth quickly attains a large size. The most indolent growths are of types (b) to (e) above, the more active ones of types (a) (f) and (g) Mitotic figures are scants in most meningiomas

(2) Invasiveness

While most meningiomas are benign" in that they are slowly growing circumscribed tumours curable by adequate local removal, others are malignant in that they invade surrounding tissues and on rare occasions metastasize. These could properly be called 'meningiosarcomas'

(a) Invasion of the skull

This takes place in perhaps 1 in 5 of the clinically important intracranial meningiomas The growth extends into the bone canals and diploic spaces and usually excites osteoplastic thickening and the formation of an external boss composed of new-formed bone permeated by meningiomatous tissue Good reviews and case reports include those of Cushing Penfield Rand, Cope, Grant, Taylor, Kolodny, Bernstein, Rowbotham and Money Most meningiomatous hyperostoses occur in the vault of the skull, but the orbital plates and other parts of the base may be affected (Winkelman, Meadows and Case II above) Rarely, as in cases described by Cushing and by Grant, meningiomas extend beyond the bone and infiltrate surrounding soft tissues such as the temporal muscle Spinal meningiomas do not cause vertebral hyperostoses, because the dura is unattached to the bone

(b) Invasion of the brain

Invasion of the brain, chiefly along the perivascular spaces is less frequent I have seen it in two cases and it is depicted by Bernstein and by Kalbifeisch and Grebe, who also saw invasion of the Gasserian ganglion

(c) Invasion of the dural venous sinuses

This was observed by Towne and by Kalbsleisch and Grebe In one of Towne's cases the growth extended down the jugular and innominate veins into of small blood vessels Hence the grains are nearly all spherical and only rarely cylindrical, they are similar to the sand grains of the normal meninges pineal gland, choroid plexus and brain Some calcified meningiomas are plainly visible in skiagrams

(d) Fibrous form

Some tumours are predominantly fibro collagenous, with or without whorling or sand grains and microscopically resembling hard less often soft fibromas Collagen fibroglia and elastic fibres are present. Dense hyaline change is frequent, either in discrete spherules or in irregular trabeculae.

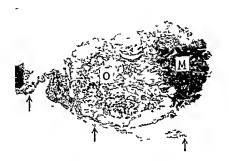


Fig. 356—Case III Ossified meningioma M = meningiomatous part O = ossified part Arrows denote spinal dura mater (× 4)

(e) The ossified form

This is exemplified in the following case

Case III — Female 41 Surgical removal of hard well defined ovoid intrathecal tumour 15 centimetres in diameter III Isitology, (Fig. 356)—One half of tumour consists of 15 pecal rather cellular meningioma of fibrous tip e with many scattered psammoma bodies the other half of osteoid tissue and bone with areas of haemopoietic bone marrow Transitions from meningiomatious to bony tissue are evident early ossification proceeding especially in psammomatous for

(f) Angiomatoid form

Some tumours are richly vascular showing plentiful thin walled vessels irregularly distributed through more diffusely cellular growth. All gradations are seen between typical meningiomas and predominantly angiomatous growths (Wolf and Cowen)

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the superior vena cava. Local protrusions of para sagittal growths into the superior longitudinal sinus are not unusual when searched for. I have seen several examples in surficially removed specimens (See also Fig. 350)

(3) Metastasis

In view of the invasion of the venous sinuses by meningiomas, metastasis to the lungs might be anticipated Actually however, this occurs only very rarely The clearest examples are those reported by Jurow and by Hamblet In a negress aged 72 who died of pneumonia Jurow found two microscopically typical intracranial meningiomas with multiple small metastases of similar structure (including granular calcification) in the lungs Hamblet saw 8 metastatic nodules of menin gioma in the liver of a Chinese male aged 41 Jurow cited several other reported instances but none as conclusive as his own. Another possible example of pulmonary metastasis from meningioma was that reported in 1886 by Power a woman aged 25 who had had hemiplesia and fits for many years was found to have a fibrosarcoma of the dura excavating the brain and eroding the parietal bone and a small tumour of similar structure at the apex of the left lung

The diagnosis of the four tumours reported by Russell and Sachs as fibrosareoma of arachnoidal origin with metastases is dubious. The tumour in their first case was almost certainly carcinoma of the lung in their second case a huge hepatic tumour may have been the primary one and in their third and fourth cases the anaplastic growths involving both brain and meninges are of

uncertain nature

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suggests the possibility that hormonal disturbances may play a part in the genesis of myomas This supposition is supported also by the frequent multiplicity of

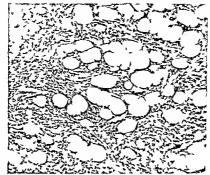


Fig 357 -Fat cells in a uterine myoma (x 60)

the growths, their usual development during the sexually active period of life, their frequent presence in patients with oestrogenic tumours of the ovary (see Chapter 29), and possibly by the experimental production of uterine and peritoneal



Fig. 358—Epithelioid appearances and hyaline change in a uterine myoma. (× 150)

[&]quot;fibroids" (doubtfully related to human myomas however) by prolonged administration of oestrogens (see Chapter 4) There is need of further careful

CHAPTER 47

LEIOMYOMA AND LEIOMYOSARCOMA

THE TUNOURS of non strated muscular tassue will be considered briefly under the following regional heads those of (a) the uterus (b) the alimentary canal, (c) the shin (d) other parts

LEIOMYOMA AND MYOSARCOMA OF THE UTERUS

Adequate descriptions of the main characters of the common uterine myomas arguen by many writers e g Bland Sutton or Novak and need not be repeated here I comment only on certain special points

- (1) Some peculiarities of structure of myemas
- (a) Heteratopic tissues in myomas

Myomas occasionally show fat cells mingled with the muscular tissue and these sometimes become so abundant that the tumour appears to the naked eye like a lipoma rather than a myoma (Bland Sutton Williamson and Brockman, and Fig 357) Calcified myomas rarely undergo ossification (Glendining)

(b) Peculiar appearances of altered muscle fibres

These occur especially in oedematous or cystic myomas by contraction of groups of muscle fibres into compact masses of plump rounded or ovoid cells or by hyaline collagenous change isolating groups of altered muscle fibres. The appearances produced may superficially resemble those of epithelial masses (Fig. 358), but transitions between the altered tissue and more typical bundles of muscle fibres are usually to be found

(c) The relationships of my amos to the surrounding my ametrium

These deserve closer study The usual view that myomas are encapsulated growths sharply distinct from the myometrium needs revision for while this may be true of large tumours it eertainly does not apply to many small ones. Minute myomas even when apparently well circumscribed to the naked eye are often not sharply separable from the surrounding muscle microscopically the appearances suggesting rather that the early growth of the tumours involves extending myomatous transformation of a small region of myometrium as well as intrinsic proliferation. Beingn myomas are not invasive in the strict sense but they sometimes form polypoid projections still clothed by intima, within veins (Scyler). Frank is use of the term fibromyosis to describe a peculiar plexiform endolymphatic growth is unfortunate in that it implies a myometrial origin the growth in question more closely resembles endometrial stroma.

(2) Evidence of hormonal factors in the causation of myomas

The endocrine control of the structure and activity of the myometrium at once

The following three necropsy cases illustrate these and other features of the disease

Case I (Willis 1934 p 438) - Female 46 History - Hysterectomy at end of 1929 fibroids , then well until September 1931 when cough and pain in chest developed Necropsy (May, 1932)-Huge tumour replacing middle lobe of right lung a small turnour in left lung All other organs clear Histology-Well differentiated leiomyosarcoma (Fig. 359)

Case II (Willis 1934 p 438) - Female, 28 Necrops) - Leiomyosarcoma of uterus with metastases in peritoneum liver rib and cranial dura mater

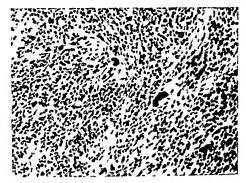


Fig 360 - Case III Pleomorphic-celled part of uterine leiomyosarcoma (× 180)

Case III (Willis 1941 No 392) - Female 47 History-During convalescence from hysterectomy for fibroids patient complained of pain in back and skiagram showed destructive lesions in lumbar vertebrae Re-examination of uterus then disclosed a crescentic area of soft sarcoma in one of the myomas A few weeks later patient died suddenly Necropsy-Tumour deposits in retroperationeal lymph glands whence gross polypoid invasion of ovarian and inferior mesenteric veins and of inferior vena cava large tumour embolus arrested in man left pulmonary artery Multiple metastass in lungs and many vertebrae Histology—Parts of growths show well differentiated leiomyosarcoma other parts poorly differentiated pleomorphic-celled sarcoma (Fig 360)

(a) Age incidence

Most leiomyosarcomas are in middle aged or elderly people but young women are not exempt (e g Case II)

(b) Structure

The terms ' malignant myoma' ' metastasizing fibroid' etc., which have often been applied to these growths, indicate the high degree of cellular inquiries into the reproductive and menstrual histories of patients with myomas, into the frequency with which these tumours are associated with significant ovirian abnormalities, and into the frequency of myomas in patients with mammary cancer

(3) Secondary tumours of uterine myomas

Myomas may be invaded by neighbouring growths such as uterine or ovarian careinomas (Glendining Cullen) or from the peritoneal deposits of gastice or other catenomas (Schmort, Davidsohn) or they may be surrounded by such growths but not invaded (Walter) Blood borne metastases from remote primary growths are occasionally found within myomas e g from careinoma of the lung melanoma or mammary careinoma (Schaper Schmort) and my Case XV Chapter 13)

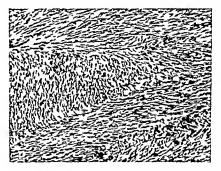


Fig 359 - Case 1 From pulmonary metastasis of leiomyosarcoma (150)

(4) Leiomyosarcoma or malignant myoma of the uterus

Most sarcomas of the uterus are myosarcomas and many of these arise in pre-existing myomas. The grounds for this conclusion are that in some cases the sarcoma is found in only a part of an otherwise ordinary looking myoma (Case III below) that in nearly all cases of sarcoma the uterus is myomatous and that in not a few of these cases—fibroids—are known to have been present long before the increase in size or aggravation of symptoms attributable to the sarcoma. In many cases however, it is impossible to prove whether the sarcoma arose in a previously benigh tumour or whether the tumour was malignant from its inception. In some instances leiomyosarcomatous metastases have developed in patients who had previously undergone hysterectomy for supposedly simple. Throids

good and myofibrils can be clearly demonstrated, distinction between myoma and neurilemmoma may prove impossible. Small firm, well defined pale nodules in the stomach wall are fairly common incidental findings in necropsy work, these are found to be either myomas or neurilemmomas (q v)

Leiomy osarcoma of the stomach is rare, according to Golden and Stout, the proportion of malignant to benign myomatous tumours of the stomach is about 1 to 8

(2) Myomas and myosarcomas of the intestine

These are rather less eommon than those of the stomach but a higher propor Iton of them are sareomatous (Golden and Stout). The small intestine is more frequently affected than the large intestine, and the most important results are either intussusception with obstruction or ulceration and haemorrhage (Smith, Foshee and McBride Golden and Stout, Foster). Meckel's diverticulum is an oceasional site of origin (Nygaard and Walters). The following Cases IV, V and VI exemplify fatal haemorrhage from benign growths, and Case VII leiomyosarcoma of the large intestine.

Care IV — Female 76 History — Admitted to hospital in extremi passing large amounts of fresh blood by bowel and died the following day Necrossy — A smooth spherical tumour 9 centimetres in diameter was attached to middle of small intestine and lay in mesentery. Intestinal mucosa was ulcerated over an area 1.5 centimetres in diameter and a small aperture led from base of ulcer into centre of the tumour which consisted of a thin shell of white tissue enclosing a large degenerated cavity full of blood clot Histolory—Bennen leonwoma

Case V—Female 46 Histori—Several attacks of melaena over a period of 7 months Necropsy—I atteral wall of second part of duodenum contained a firm well circumscabed lobulated tumour 4 centimetres in diameter hour glass shaped with ulcertation of the mucosa overlying the internally projecting half Histology—Benigm leionnyoma

Case VI — Male 47 History — Recurrent recent malaena Necropsi — Ovoid tumour 5 centimetres in diameter attached to antimesenteric aspect of ileum 4 feet above caecum small ulcerated area of growth presented in bowled Histology — Benign leiomyoma with much fibrosis

Case VII (Willis 1934 p 437)—Male 44 (Chinese) History—Constipation and passage of blood and mucus per rectum for 10 months palliative colostomy Necropsy—Bulky lobulated fairly well defined tumour of rectum with ulceration and perirectal cellulitis multiple large well defined spherical white metastases in liver only Histology (Fig. 361)—Partly well differentiated typical leiomyomatious structure partly disorderly pleomorphic-celled sarcoma

LEIOMYOMAS AND MYOSARCOMAS OF THE SKIN

(1) Multiple dermal leiomyomas

These have long been known to dermatologists. They are probably not true tumours but rather hamartomas or minor malformations with excessive development of the arrectores pilorum muscles they often appear at an early age frequently in regional groups they grow slowly, seldom to sizes more than I centimetre in diameter, and they may remain stationary or retrogress

differentiation which they may attain But of course a tumour which invades or metas tasizes is a sarcoma, however well differentiated in structure Moreover in most eases adequate microscopical study of several different parts of a growth will usually lead to a correct diagnosis of innocence or malignancy . sarcomas usually show anaplastic areas with nuclear abnormalities and excessive mitoses A cellular leiomyomatous growth which arouses the pathologist's suspicion but of the malignancy of which he feels uncertain is usually benign. Much less commonly, a tumour adequately studied histologically and regarded as benign may prove its malignancy by its behaviour Stemer has reviewed such cases in which a tumour has been composed, 'in both the primary growth and its metastases of benign appearing fully differentiated smooth muscle cells and dense connective tissue but his view that this distinguishes it from primary leiomyosarcomas of the uterus and from sarcomas arising in fibromyomas is unwarranted. Steiner's ease was of interest in that, as in my Case I a myomatous uterus not clinically suspected of malignancy produced massive well differentiated metastases in the lungs

(c) Metastases

As with most other kinds of sarcoma the lungs are the principal sites of metastasis. Other organs may, however, be affected e.g. in my cases the liver bones and dura mater, in Finlay's case the heart and kidney. Lymph nodal deposits were present in the cases of Finlay Schreine. Steiner and in my Case III.

LEIOMYOMA AND MYOSARCOMA OF THE ALIMENTARY TRACT

Leiomyomas of the oral carity are very rare (Stout) Those of the oesophagus are less uncommon as incidental necropsy findings I have encountered 3 specimens, the largest 2 centimetres in diameter in a woman of 52 years Rose sink 4 oesophageal myomas with obstruction in a man of 74 years he reviewed 48 reported eases, of which the tumours were recorded as single in 35 and multiple in 11

(1) Myomas of the stomach

Gastric myomas are far from rare (Golden and Stout Muir Ball). They are well circumscribed growths which project either into the stomach or into the peritoneal cavity. In the latter situation they often attain a great size. In 1930, I recorded a subserious gastric myoma which was known to have been present for at least 5 years and which finally weighed 900 grammes and there are many recorded instances of tumours far larger than this. Peptic ulceration of the overlying mueosa and often of the tumour itself is a frequent complication of intragastric growths, these may also eause partial invagination of the stomach wall or may cause ball valve obstruction of the pylorus. The smooth outlines of the filling defect seen in stangtams following opaque meal may suggest a being growth. Many instances of successful surgical removal have been reported. Though well defined to the naked eye, the tumours are often not encapsulated but merge with the museular coat of the surrounding stomach wall. Distinct regimentation of nuclei may be present and may cause confusion with neunlemmoma (see Golden and Stout). Indeed unless fixation has been

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(2) Solitary myomas

Solitary myomas of the skin or subcutaneous tissues have been less well recognized though they are probably as frequent as the multiple form. Stout has given a valuable review of these tumours

(3) Sex

Multiple dermal myomas occur in males about twice as frequently as females, solitary myomas affect the sexes about equally

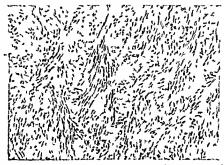


Fig. 361—Case VII Well-differentiated myomatous structure in hepatic metastasis of leiomyo sarcoma of rectum (× 150)

(4) Age

In three quarters of the cases the multiple growths appear before the age of 30 less than one half of the solitary growths develop before 30 years Many of the tumours are of slow growth and long duration

(5) Site and origin

The commonest sites are the face inpple area extensor surfaces of the limbs and the external gentalia. Those situated in the dermis—and this applies to most of the multiple grow ths—clearly arise mainly from the arectores pilorum mulcles while those of the subcutaneous tissue usually solitary more often take origin from the musculature of blood vessels. Other possible sources of tumours in particular situations are the non striated muscles of the nipple and areola scrotum and penis. Tabba and penianal region.

(6) Structure and growth

Dermal myomas though often fairly well defined, are usually not encapsulated

present, including renal cysts or hamartomas, cutaneous "adenomas", hetero topic islands of neuroglia in the meninges, malformations of the pancreas, of the heart itself, eleft palate, etc. Many cases are still born or die in infancy or child hood, but survival into adult life is possible, the oldest recorded patient being 35 years old (Steinbiss). The myocardial lesions show characteristic large vacuolated "spider" cells which contain abundant glycogen and often show radial or transverse striations of their peripheral cytoplasm. No instance of progressive growth has been reported, and the largest tumours' rarely exceed 2 centimetres in diameter.

The pleomorphic celled growth described by Bradley and Maxwell as a "rhabdomyosarcoma" of the heart with metastases in lungs liver and kidneys, is of doubtful nature, and no cross striations were found in the tumour cells. The nature of the tumour in a woman aged 37 reported by Larson and Sheppard as a rhabdomyoma of the heart with sarcomatous extensions" is doubtful, insufficient details are given, and the transverse striations depicted might be arte facts and not true muscular strate. The spindle celled sarcoma of the heart reported by Muller (Case 4) as "probably an undifferentiated rhabdomyosarcoma' showed only 'a suggestion' of cross-striations in its cells

RHABDOMYOSARCOMAS DERIVED FROM SKELETAL MUSCLES

The rarity of undoubted rhabdomyosarcomas of adult voluntary muscles is preciously noteworthy. The earlier literature (Benenati , Wolfensberger) contains many references to "rhabdomyosarcomas", but most of these were in the testis, kidney, uterus or other sites where teratomas or mixed tumours occur, and very few primary growths of skeletal muscles were recorded. Some of the more recently reported and acceptable cases may be briefly mentioned.

Wolbach (1928) described a rhabdomyosarcoma of the spinal muscles in a girl aged 4, and studied the mode of development of the cross striations in the tumour cells Hirsch (1929) reported a tumour of the muscles of the leg in a boy aged 7, with metastases in many lymph glands, lungs and pelvic viscera, the cells contained abundant glyeogen, and cross striated cells were present in the metas tases In a man aged 21, Hirsch (1931) also saw a huge tumour of the neck which he regarded as a mixed tumour of the thyroid containing striated muscle fibres but, as the cervical muscles were extensively involved and as the supposed thyroid elements in the tumour were probably anaplastic sarcomatous tissue, the diagnosis of rhabdomyosareoma of the muscles appears more probable Cappell and Montgomery (1937) described two polypoid rhabdomyosarcomas of the palate one in a girl aged 10 who died 7 years later with metastases in lungs and many lymph glands and the other in a girl aged 9 who died 6 years later with signs of pulmonary metastases In these eases the polypoid masses elothed by intact epithelium, recalled the appearance of the grape like sariomas of the vaging in children Two other eases of palatal rhabdomyosarcoma are referred to by Cappell and Montgomery, one reported by Nicory in a girl aged 5, the other by Martin and Alexander in a girl aged 6 who died later from recurrent growth and deposits in the cervical lymph glands These palatal tumours presumably arise from the pulatal muscles, though this has not been proved. A huge

CHAPTER 48

RHABDOMYOMA, RHABDOMYOSARCOMA AND RHABDOMYOBLASTIC MIXED TUMOURS

SEVERAL uncertainties combine to confuse discussion of tumours consisting of, or containing rhabdomyoblastic elements. Relatively rarely is the adult skeletal musculature of the body clearly and unmistakably the origin of a rhabdomyosarcoma. Most rhabdomyomatous tumours are either embryonic growths derived from immature myoblastic or undifferentiated mesenchymal tissue or mixed tumours in which other heterotopic tissues besides muscle are differentiated. Introduction of the term 'myoblastoma has added to the confusion for its use is not uniform and it has often been applied far too uncritically. The so called 'rhabdomyomas' of the heart, with very rare and doubiful exceptions are not tumours at all but malformations.

A systematic account of rhabdomyoma is therefore impossible. I propose to deal with this heterogeneous group under the following headings

- 1 Rhabdomyoma' of the heart
- 2 Rhabdomyosarcomas derived from skeletal muscles
- 3 Myoblastomas '
- 4 The grape like vaginal sarcomas of children
- 5 Rhabdomyomatous tumours of the bladder
- 6 Rhabdomyomatous tumours of the male genitalia
- 7 Mixed mesenehymal tumours of the uterus
- 8 Rhabdomyomatous tumours of other parts
 9 Rhabdomyoblastic tissue in embryonic renal and hepatic tumours and
- in teratomas
- 10 Rhabdomyomas in animals
- 11 General conclusions regarding the histogenesis of rhabdomyoblastic tissue in tumours

The discussion of 4 and 7 will involve consideration of the whole of these groups of tumours even though some of their members lack recognizable muscle for we cannot artificially divoree those in which myoblastic tissue has been demonstrated from those appearing to lack it. It is certainly a frequent, and sometimes a predominant, component of these tumours.

RHABDOMYOMA OF THE HEART

The so-called eongenital rhabdomyomas of the heart well reviewed by Steinbiss Farber and Labate ean quickly be dismissed they are not tumours but developmental anomalies. In most cases they are visibly multiple or accompanied by microscopic foei of similar malformed tissue in other parts of the heart as in Farber's ease or the entire myocardum may be diffusely affected as in Schminicke's case. In many cases the patients are aments or epileptics with tuberous selerosis of the brain and other developmental anomalies also are often

striations can be found, the muscular nature of a tumour cannot be affirmed with certainty I have examined many pleomorphic celled sarcomas involving muscles in adults, in the hope of being able to demonstrate their rhabdomyomatous nature, but so far in vain

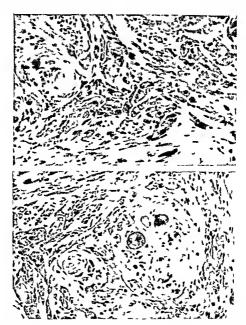


Fig. 364—(Dr L M Hanksley's specimen) Lingual myoblastoma from a man aged 60 showing preservation of general pattern of lingual musculature by the abnormal cells and the presence of Cohnheim's areas in some of them (×200)

As MacCallum pointed out, altered fibres of the invaded muscle may be mistaken for tumour cells. This source of error, of which some writers have been unawrie is excluded in MacCallum's specimens—rhabdomyosarcomas of the brachialis and gastrocnemius muscles in a man aged 59 and a woman aged 70—for mitoses were seen in striated tumour cells. Some of Rakov's figures of fibrils and cross striations are not wholly convincing, and, in any case, he gives

spindle celled sareoma of the middle car in a boy aged 5 described by Maconie was found by J Swijda to be a rhabdomyosarcoma (Fig 363) it may well have arisen from the polatal muscles around the Eustachian tube

The youth of the patients in all of the foregoing cases of rhabdomyosarcoma is noteworthy—it raises the question whether the tumours arose from mature differentiated muscle fibres or from still immature embryonic myoblasts, a question all the more pertinent in view of the doubtful and limited capacity of striated



Fig. 363—Rhabdomyosarcoma of middle-ear region in a boy aged 5 (Maconie's case re investigated by Svejda R C S Museum Accession No 296 iron haematox) lin stain) (× 800)

muscle for proliferation once it has attained adulthood. The resemblance of the palatal tumours to the vaginal ones both in gross and microscopie features including the presence of immature myxoma like tissue strengthens the idea that the former probably are as the latter certainly are (see below) truly embryonic tumours arising from young tissue which has never differentiated. On the other hand several workers (e.g. MacCallium Rakov) have shown

that some pleomorphic-celled sareomas in adults are rhabdomyosareomas in which anaplasia has largely deprived the cells of striations and other distinctive structures. Suggestive features are long strap-like cells with longitudinal fibrils which show up sharply in carefully differentiated iron haematovylin preparations sharp zig zagging of these cells and fibrils and large rounded cells with one or several central nuclei and strongly cosinophil cytoplasm. These features in a pleomorphic-celled sareoma justify meticulous search for strate which may be found either as typical transverse strations in fusiform or strap like cells, or as regular beading of individual longitudinal fibrils or as radial strate or fine peripheral hatching in the large rounded cosinophil cells. Unless distinct

plainly that the latter are not, as the name implies, immature cells undergoing differentiation but altered derivatives of the muscle fibres. True myoblasts in the embryo do not, at any stage, resemble Abrikossoff's "myoblasts", but similar appearances are seen in states of degeneration and regeneration of skeletal muscle following injury (see below)

Different usages of the name "myoblastoma" also cause confusion Most writers have applied the term particularly to the benign lesions composed of large granular cells, but others have included also anaplastic malignant growths of supposed muscular origin Thus Klemperers first case was a pleomorphic celled streoma Cappell and Montgomery s "myoblastomas" of the bladder and of



Fig. 366—(Colonel W.F. Harre) s specimen.) Cutaneous myoblastoma of the knee region from a man aged 32. Tumour had been present 11 years was 1.5 centimetres in diameter was restricted to dermis and subcutis and unattached to muscle and had recently suffered slight superficial ulceration. (× 200)

the spermatic cord were predominantly spindle celled growths, and their ' malig nant myoblastoma" of the tongue was also an anaplastic spindle-celled sarcoma quite unlike the benign lingual myoblastomas" of Abrikossoff Tumours dubbed myoblastomas" in situations where no muscle is present

Tumours dubbed myoblastomas" in situations where no muscle is present of course cannot show transitions as conclusive evidence of their supposed muscular origin and it is particularly significant that in none of them has unequivocal ross striation been observed, in striking contrast to their supposed counterparts.

the tongue. What then is the cyclence suggesting their muscular nature?

mistely this—that they consist of cells more or less resembling the large granular
unaw? on strated cells of growths of known muscular origin. I agree with Gray
brachiar unfield that this resemblance however close does not prove identify
for mitoammed three growths from the skin of the thigh and one from the breast
fibrils and cucture identical with that depicted in 'myoblastomas' (Fig. 366),

no details of the individual cases from which his figures came. It is significant that most of the individual rhabdomyosarcomas with beautifully striated cells bave come from children or adolescents, and that such tumours are relatively very rare in adults. This fact should engender great caution in making a diagnosis of rhabdomyosarcoma in in adult, save on unimpeachable grounds.

MYOBLASTOMA '

Under the title "Myoblastenmyome (later reduced to myoblastoma" by tongue and other parts, consisting of large rounded ovoid or clongated cells with acidophil granular cytoplasm which in some tumours showed longitudinal and cross striations and transitions to undoubted muscle fibris but in other tumours showed no such evidence of their origin (Tigs 364, 365). Although Abrikossoff

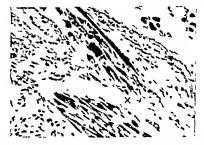


Fig. 365—Lingual myoblasioma from a boy aged 8 Transitions from normal to abnormal muscle fibres are visible at X (× 200)

is credited with priority of recognition of a muscular origin of growths of this kind, a similar lingual tumour was clearly depicted and described as a rhabdo myoma" by keynes in 1926 Subsequent writers (Klemperer Gray and Gruen feld Horn and Stout Crane and Tremblay) added to the records of lingual

myoblastomas" and applied this name also to an increasing number of tumours in other situations including sites such as the skin and breast which normally contain no striated muscle, where it was assumed that the tumours arise from embryonal rests of aberrant myoblastic tissue (Horn and Stout)

(1) Possible fallacies regarding myoblastomas

Both the name myoblastoma and the identification of many of these growths as of muscular nature are open to serious question. Where as in the tongue and occasionally elsewhere the growth is undoubtedly muscular in origin the transitional forms between strated muscle fibres and the myoblasts show

of normal looking fibres with swollen protoplasmic granular masses, transition forms between normal and granular cells and, in one specimen, gentle transition from the normal musculature to the altered tissue, the latter retaining the pattern of the former (See Figs 364, 365)

The fact that the tongue, an organ which is frequently and repeatedly subjected to small injuries, is by far the commonest site of these growths, suggests their traumatic origin, a suggestion strengthened by their regularly superficial situation on the dorsum or along the margins of the organ. Some of the extra lingual growths also have shown features strongly suggesting a traumatic or inflammatory

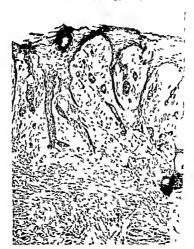


Fig. 367—Irregular overgrowth of the epithchum overlying a lingual myoblastoma same specimen as Fig. 364 (× 60)

from

origin 'e g the 'myoblastoma' of the thoracic wall reported by Grayzel and Friedman a stony hard mass 27 centimetres in diameter, did not increase in size during the several months it had been noticed inflammatory leucocytes were present in it and the 'myoblasts' merged with well preserved muscle fibres. One final feature of 'myoblastomas', which has some bearing on the present

One final feature of 'myoblastomas', which has some bearing on the present discussion is the frequent presence of irregular hyperplasia of the epithelium overlying them when they occur in the tongue or other immediately subeputhelal sites. This hyperplasia, observed by most writers on the subject and depicted in Fig. 367, may easily be mistaken for early invasive carcinoma. If 'myoblastoma

and in none of these could I see any reason-except cytological resemblance to the lingual growths-to suppose them to be of muscular nature. It has been admitted by several writers on the subject that they have confused vanthomatous collections of foam cells with myoblastomas" since which reporters of these growths have been careful to say that their myoblistoma' cells were not vacuolated but granular and that Sudan III and other fat stains gave negative results Much has been made of the presence of glycogen in the large granular cells, but this finding is of little significance for real myoblasts may contain little or no glycogen, and other kinds of cells, including of course epithelial cells. may contain large quantities. I have not seen a specimen of congenital epulis or 'myoblastoma" of the gums of a new born infant, but from perusal of the several reports of this condition (Cuelen Meyer Crane and Tremblay) its muscular nature seems to me very dubious. Indeed, I am unconvinced of the muscular nature of any of the extra muscular myoblastomas" reported by Abrikossoff Ceelen Klemperer Horn and Stout and Crane and Tremblay who I think have fallen into the time honoured error of construing resemblance as identity Some of these writers evidently harboured slight doubts of their own diagnoses witness the frequent use of such phrases as 'appear to be closely resemble' or " may be classified as myoblastoma

(2) Neoplasia or regeneration?

Returning now to the benign large granular celled myoblastomas of the tongue or of other skeletal muscular tissue in the lip cheek, limbs or elsewhere, there are strong grounds for doubting whether these are true neoplasms. In spite of the undifferentiated appearance of their cells and their not infrequent "infiltration of adjacent tissues they are benign neither ulcerating metastas izing nor recurring after removal The abnormal cells show no mitoses and the lesions usually remain quite small even after prolonged duration. Crane and Tremblay's tabular review shows many cases of lingual 'myoblastoma which were only small nodules or 1 or 2 centimetres in diameter after several years duration-18 years in the case of Martinez Of course small size and long duration do not exclude neoplasia but they certainly increase the suspicion that the lesions may be non neoplastic. Then many reporters of lingual lesions have seen clear transitions from normal skeletal muscle fibres to myoblasts fibres often ending in bulbous granular swellings identical in appearance with the cells of the bulk of the lesion-an extraordinary relationship if this is indeed a neoplasm. And lastly, granular changes resembling those of myoblastomas." are sometimes seen in degenerative or regenerative lesions of striated muscle fibres Thus Meyer depicted the typical appearance of myoblasts in damaged muscle fibres in an abdominal scar Gray and Gruenfeld saw the same in association with an ulcer of the tongue and I have seen similar appearances in muscles after injury and after the application of radium. The varied appearances of degener ating muscle fibres following crushing injuries or ischaemic necrosis and of the regeneration sprouts which grow into the old sarcolemmal sheaths as depicted by Le Gros Clark are pertinent in this connexion

I have examined 8 specimens of lingual myoblastoma all of which appeared to me clearly to be areas of altered muscle fibres. They often showed continuity

In the following ease the tumour, though not polypoid or intra vaginal, contained rhabdomyomatous elements and almost certainly belonged to the group of tumours under discussion

Case II—History—After intermittent abdominal pain for 12 months a girl aged 6 years was admitted to hospital with a palpable large lower abdominal tumour X runardation failed to effect any improvement and she died 4 months later. Necropsy—A large lobulated growth filled the pelvis, compressed the intact bladder uterus and vagina interiorly and the rectum posteriorly and invaded the pelvic and iliac muscles but not the bones. Many pelvic and abdominal lymph glands contained large deposits of growth and there were scattered metastases in the peritoneum and in the lungs. Histology—Cellular sarcoma containing plump spindle cells large irregular multinucleated cells with cosmophilic cytoplasm many long cylindrical cosmophilic fibres closely resembling young skeletal muscle fibres with few faint striations discernible here and there and areas of oedematous or mixoma like tissue.

(1) Age

With rare exceptions, these tumours make their appearance before the age of 5 and in about one half of the cases before the age of 2 Dugge, however, refers to 2 reported cases in girls of 15 and 17 years

(2) Site

Any part of the vaginal walls may be the starting point of the growths, but the most common site is the upper part of the anterior vaginal wall—20 of 33 cases in Adler's review Occasionally the origin of the growth is close to the vulva, e.g. from the hymen in Amolsch's case. The base of the bladder is often implicated, and the tumour may project into it as well as into the vagina, as in my Case I

(3) Appearance

Botryoid 'and "grape like" well describe the characteristic polypoid oedematous masses of growth which distend the vagina and project externally The tumours also infiltrate the tissues of the pelvic floor and fill the pelvic cavity compressing the bladder anteriorly and the uterus usually laterally or posteriorly

(4) Microscopic structure

This is fairly characteristic. The bulk of the growths usually consist of a mixture of oedematous or myxoma like tissue and more cellular spindle celled or pleomorphic celled sarcoma, scattered through which there may be a few or many cells with recognizable cross striations. Thorough search in well stained iron haematoxylin preparations may be necessary to discover them. Some timours show no recognizable muscle elements appearing simply as embryonic cellular sacromas. The growth itself includes no cpithelial elements, but the surfaces of the grape like masses are clothed by vaginal epithchum which dips down deeply into the intervening crevices of the tumour. The tumour and the overlying intact epithelium form an organized structure and gross ulceration is rare Cartilage or bone has not been described in these growths though it is often present in the rather similar botryoid sarcoma of the cervix in adults (see below). Nagel reported a highly vascular angioblastic sarcoma of the vagina of an infant which probably belongs in this group.

is indeed a neoplasm, this striking overgrowth of the epithelium is difficult to account for But if it is a trainmate inflammatory or degenerative k-sion content firstative epithelial hyperplassa in the same area is readily understandable

For the foregoing reasons, I join the considerable group of pathologists who doubt the neoplastic character of the beingin 'myoblastomas of the tongue and of other skeletal muscles. I believe these lessons to be the result of injury to muscle fibres with subsequent degenerative or regenerative changes. Large granular masses of sarcoplasm in visible continuity with residual muscle fibres strongly suggest regeneration sproust comparable with those observed by Le Gros Clark in crushed muscle. Perhaps thermal or chemical injuries also may evoke the peculiar reactionary overgrowth sent in the so called myoblastomas. Perhaps the granular 'myoblasts' include also in wandering macrophages, distended by glycogen and other products of the degenerating muscle fibres and assuming clongated forms within the sarcoleminal sheaths of the damaged fibres which they have invaded.

(3) Personal conclusions regarding myoblastomas '

- (i) The benign granular celled 'myoblastomas' of the tongue and of other skeletal muscular tissue are not tumours but degenerative or regenerative lesions of muscle fibres II however the occasional existence of true neoplasms of this appearance were to be proved they should be called rhaddomyomas
- (ii) Lessons of similar appearance in tissues where no striated muscle is present should not be called myoblastomas, their muscular nature is unproved
- (iii) The term "myoblastoma is unnecessary for and should not be applied to, malignant tumours of proved museular origin these are rhabdomyo sarcomas. If anaplasia deprives the cells of a rhabdomyosarcoma of the distinctive characters of striated muscle cells especially cross striations, then certain histological recognition of the nature of the tumour becomes impossible it is better frankly to recognize this difficulty than to take refuse in a num.
- (a) The term myobiastoma' should therefore be discarded it is only serving to perpetuate several erroneous or dubious concepts

THE GRAPELIKE SARCOMAS OF THE VAGINA IN CHILDREN

One of the earliest reports of these rare tumours was that of Marsh and Beck (1874) McFarland (1911) reviewed 32 of the earlier reports Adler (1928) tabulated records of 41 cases in the German literature, and Dugge (1930) gave a good outline of the subject. In the following case the tumour though typical in other respects was predominantly vessed urethral this indicating the essential identity of this group of tumours and the vessed ones described below.

Case I—Hutory—A neglected child 2 years old with no available history was admitted to hospital because of a bulky polypoid growth protruding from the vagina. This progressed and the child died 2½ months later. Neveropia—The growth replaced the base of the bladder and urethra and protruded into the lower part of the vagina is upper vagina and uterus were intact. Histology—Vascular undifferentiated spindle celled growth replaced the vessel and urethral mucoks and only slightly invaded the surrounding muscle. The surface of the polypoid protrusions was clothed by stratified entitled.

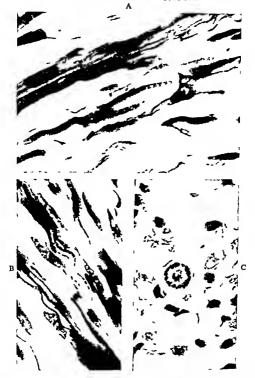


Fig. 368—Grape like rhabdomyosarcoma of bladder from a male child 18 months old Longi tudinal and cross striations were indefinite in ordinary preparations those depicted here are from carefully differentiated iron haematoxylin stained sections. A and B = longitudinal fibrils with transverse striate. C = spherical cell with marginal radial striate giving rosette appearance and a neighbouring cell with fine marginal beading. (E. Minchin & Case I) (>800)

rhabdomyosarcoma with widespread metastases in a man aged 26 Khoury and Speer tabulated 18 reported eases of rhabdomyosarcoma of the prostate, 12 of whom were children or young adults (See also Fig 369) The youth of these

(5) Metastases

Metastases have seldom been recorded. In a few cases deposits in regional lymph glands are mentioned, and in Dugge's case there were some small metastases also in the lungs. Nagel's case of highly vascular tumour showed invasion of the spinal canal and of the iliac vern and inferior vena cava, and multiple tumour emboli and metastases in the lungs. My Case II above showed lymph nodal, peritoneal and pulmonary metastases.

RHABDOMYOMATOUS TUMOURS OF THE BLADDER

Early records of tumours of this kind (cited by Monckeberg and Houette) were those of Cattani, Vincenti and Husler from boys of 12, 13 and 7 years respectively Payone's specimen from a woman aged 22, and Monekeberg's own specimen from a woman aged 23. In this last ease however, although the tumour cells resembled skeletal muscle fibres in other respects, indubitable cross strictions were not found and this applied also to two cases described by Cappell and Montgomery Shattock reported four specimens of vesical rhabdomyoma all from children three boys and a girl In all cases the tumours formed multiple sessile or pedunculated mucosal polypi clothed by epithelium involving the lower half or two thirds of the organ. In one of the boys growths were present also in the mucosa of the prostatic urethra and in the female case (one of John Hunter's original specimens, still preserved in the Museum of the Royal College of Surgeons, London) the tumours projected into the urethra. Houette gave a good description of a congenital rhabdomyoma of the bladder which showed great cellular pleomorphism and the differentiation of striated muscle fibres from undifferentiated cellular tissue. White briefly reported a myxoma like rhabdomyosarcoma from the bladder of an infant aged 20 months. The tumour in Cattam s case also was myxomatous in appearance. Hirsch and Gasser reported a rhabdomyosarcoma of the neek of the bladder in a boy aged 5 and khoury and Speer saw a similar growth which involved also the prostrite and urethra in a male infant who had had symptoms since birth (See also Fig. 368)

It must be mentioned in parenthesis here that eartilage containing or bone containing tumours of the bladder like those described by Wright Smith and Pollack are probably unrelated to the rhabdomyomas. Not need they be regarded as those writers have regarded them as teratoma. They are sarcomas or careinomas with stromal metaplasia, perhaps induced by the neighbouring vesical enthelium.

RHARDOMYOSARCOMAS OF THE MALE GENITALIA

(1) Rhabdomyosarcomas of the prostate

Of 82 reported prostatic sarcomas 'reviewed by Smith and Torgerson while those in adults were very heterogeneous and many of them of doubtful nature 25 of them were from children in the first decade and many of these were recorded as either myxosarcomas or rhabdomyosarcomas' All 6 rhabdomyosarcomas including kaufmann s 3 examples were from young subjects their ages ryinging from 9 months to 31 years. Additional reports include that of Wachs of a congenital rhabdomyosarcoma and that of Foucar of 1

tissue which replaced the endometrium from fundus to cervix but did not extend into the myometrium, microscopically this was found to be typical astrocytic neuroglial tissue with characteristic staining properties, the only other foreign tissue found was one small nodule of cartilage Orsos discussed whether the condition arose from implanted embryo tissue, from the sympathetic nerves of the uterus, or from a teratoma, and he inclined to the first view. In any case, the lesion was clearly a peculiar one and not to be included amongst the mesenchymial mixed tumours.

(f) Epithelial tissues in these growths have usually been regarded as only included endometrial or cervical epithelium, and not intrinsic constituents of the tumour tissue. Non-ulcerated botryoid growths have a complete epithelial investment, and, as in the similar vaginal tumours of children the epithelium may dip deeply into the tumours between adjacent polypi. While it seems clear that the non epithelial tissues form the essential and bulkiest part of these growths, the abundance of endometrial or cervical glandular tissue in some of them at least shows great concomitant hyper plisia if not neoplasia. Rarely, as in Nicholson's case, the uterine epithe lium is simultaneously cancerous intimately admixed with the messenshymal elements and appearing with them inmetastases. My Case IV of Chapter 31 afforded an example of an endometrial mixed tumour containing both epithelial and non epithelial elements.

(5) Histogenesis

Many workers have followed Wilms in supposing the uterine mixed tumours to arise from developmentally misplaced tissues. This view should be discarded it is discredited by the researches of experimental embigologists, and it is as unneces sary as it is improbable. The supposition that undifferentiated 'rests" of developmentally heterotopic tissues may remain in the endometrium for the whole of a woman's reproductive life, surviving multiple pregnancies, and eventually producing a mixed embryonic tumour at the age of 50 or 60 or 70 is absurd Pfannenstiel in his original account in 1892 suggested that these growths arose from the endometrial stroma and that the several heterotopic tissues developed by aberrant differentiation or metaplasia Nicholson supported this view the tumours ' can be explained on the assumption of a process of de differentiation and rejuvenescence of the stroma of the uterine mucosa" I, too, hold this opinion The endometrial stroma is a peculiar and highly labile tissue Why should it not possess wide potencies for aberrant differentiation? Indeed we need assume but little more lability in this respect than we already know obtains for this and other tissues of mesenchymal origin The metaplastic forma tion of mucoid tissue, cartilage and bone is a commonplace event in many parts of the body including the endometrium in non neoplastic states (Gierke) The presence of adipose tissue in a mixed tumour of the uterus no more presupposes a dislocated "rest" than it does in a uterine myoma. Muscular tissue then especially striated muscle is the only ingredient of mixed tumours that need excite any wonder or call for any special hypothesis regarding histogenesis. The development of muscle by aberrant differentiation in a plastic mesenchymal tumour tissue which has displayed its plasticity by producing also cartilage bone and adi pose tissue, is a much more probable event than the life long retention of rests

patients the frequent presence of undifferentiated mesenchyme like tissue as well as muscular elements in the growths, and the homology of the upper vaginal and prostatic regions together suggest that the prostatic sarcomas of children and young adults are comparable with the vaginal and cervical sarcomas of children Perhaps the embryonic mesenchyme around the upper part of the urogenital sinus is in both sexes prone to the development of embryonic tumours. It is therefore uncertain whether the prostatic rhabdomyosarcomas take origin from

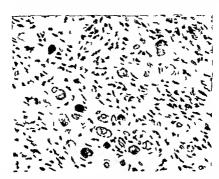


Fig. 369—Large rounded strongly cosmophit family structed cells in a rhabdomyosarcoma of the prostate from an infant 9 months old (E. Minchin's Case II) (× 350)

this mesenchyme in its immature stage or from the striated muscle fibres which are present in the capsule of the prostate and are sometimes found also even in the periphery of the gland itself

(2) Rhabdomyosarcomas of the spermatic cord and epididymis

Hirsch (1934) reviewed 12 previous reports of rhabdomyosarcomas of the cord of conditions in several of which however the tumours involved the testis so that the possibility of them having been testicular teratomas cannot be altogether excluded. Of the 12 tumours 10 were from minors including 5 children aged 5 years or under in the youngest patient the tumour had been noticed at the age of 10 months. In Hirsch's own case the boy was 16 years of age and the tumour occupied the epididymis but was separate from the testis. Again the youth of the victims of these tumours suegests an origin during early development and it remains doubtful whether the rhabdomyomatous sissue arrises from the actual

all rather diagrammatic drawings. In a subject of unspecified age Gowers saw a mass of adipose tissue containing scattered striated muscle fibres, which enveloped the nerves of the cauda equina

RHABDOMYOBLASTIC TISSUE IN TERATOMAS AND IN EMBRYONIC RENAL AND HEPATIC TUMOURS

This need only be mentioned here, details are given in the appropriate chapters. In the present connexion the occurrence of strated muscle in these growths is important in two respects, (a) because occasionally it is an abundant and conspicuous component, witness the fact that during the last century not a few of the teratomas of the testis and embryonic tumours of the kidney were called 'rhabdomyosarcomas', and (b) because it shows that rhabdomyoslasts can develop by aberrant differentiation in neoplastic embryonic tissues

RHABDOMYOMATOUS TUMOURS IN ANIMALS

(1) Multiple "rhabdomyomas" of the heart

Multiple rhabdomyomas" of the heart have been seen in young pigs (references by Farber and Feldman), and in a guinca pig (Hueper)

(2) Rhabdomyomatous tumours of skeletal muscles

These have been found in several species of fish (references by Nicory Haddow and Blake Kolmer) Feldman described and depicted two good examples from mammals, one from the leg of a 5 year old horse and the other from the prescapular region of a year old sheep He referred also to the scanty previous reports of rhabdomyomas of skeletal muscles in animals, including horse, or and chicken

(3) Rhabdomyomatous tumours in other sites

Feldman redescribes and depicts a remarkable specimen recorded by Day, one of multiple growths consisting of abundant strated muscular tissue along with scattered glandular elements in the lungs of a 5 month-old lamb. Other organs were said to be normal but the possibility remains that the growths may have been metastases from an undiscovered primary growth e.g. in the testilithey were indeed primary in the lung, they were comparable with those in Zipkin's case already referred to Feldman also mentions a rhabdomyoma of the vagus nerve seen by Gratia in an old horse but no details are available

GENERAL CONCLUSIONS REGARDING THE HISTOGENESIS OF RHABDOMYOMAS

Several facts suggest that most rhabdomyomas are embryonic growths arising from immature myoblastic tissue and not from already matured strated muscle fibres. These facts are

(I) Age incidence

With the exception of the uterine mixed tumours nearly all unquestionable rhabdomyomatous growths arise early in life. Most of the unequivocal rhabdo myosarcomas of skeletal muscles have been in children or adolescents, all of the

of embryonic tissue of multiple kinds. Case IV of Chapter 31 showed plainly the development of abundant smooth muscle from the endometrial stroma

Indeed we can go further The relationships and transitions of the different tissues seen in the mixed tumours show clearly that these do not arise as separate elements which then mix together, but that they are each and all products of the undifferentiated mesenchymal cellular myxosarcoma like tissue which is invariably present. This is the essential parenchyma of the tumours from which all the differentiated elements arise, it is neoplastic endometrial stroma which in the process of becoming neoplastic has again become embryonic and has re acquired unusual potencies for aberrant differentiation.

(6) Growth and behaviour

Both the corporeal and ecruical mixed tumours are highly malignant frequently recurring or metastasizing and this in spite of the fact that they often appear confined to the uterus when first seen. Recurrence or local metastasis is frequent in the pelvie eavity or peritoneum perhaps ligature of the tubes before performing hysterectomy and eare not to spill loose particles of growth during its performance might minimize this risk. Remote metastares are usually situated in the lungs but may occur in other parts too e.g. the kidneys and bones in Duggan's ease. Their structure is usually cellular and anaplastic, but careful studies of further necropsy cases is necessary to determine whether all the potencies of the tumour tissue for diversent differentiation may reappear in metastases

RHABDOMYOMATOUS TUMOURS OF OTHER PARTS

Very rarely a rhabdomyoma or rhabdomyosarcoma of some other viscus is reported This may be in an organ where striated muscle is present as in Wolfen berger's case of rhabdomyosareoma of the oesophagus or it may be in a part where normally there is no striated muscle. Thus Helbing described , a rhabdomyoma replacing the lung of a man aged 23 and Zipkin described a similar growth in the lung of a 33 weeks foctus in which bronchi traversing the striated muscular tissue themselves had striated instead of smooth muscle in their walls. In both of these eases the lesion was probably a malformation rather than a true tumour, but in a man aged 52 McDonald and Heather saw a pulmonary rhabdomyosarcoma with massive polypoid extensions through the pulmonary veins into the left atrium. Needless to say in such a case as this great care must be taken (a) to exclude the possibility of the growth being 1 teratoma with plentiful muscular elements (b) to exclude the possibility of it being a metastasis e.g. from a small testicular tumour and (c) that the cross strictions are genuine ones and not merely artefacts produced by shrinkage fragmentation or concerting like buckling of cells. In a negress aged 38. Sailer saw a pleo morphic celled rhabdomy osarcoma of the breast with distinctly cross striated cells in the pulmonary metastases. The cross structions in the rhabdomy oblastic cells seen by Govan in two mixed tumours of the breast were less distinct being restricted to beaded cell margins. Masson and Martin reported rhabdomyo sarcomas of peripheral nerves in three young subjects with neurofibromatosis it is regrettable that the micro figures depicting these extraordinary tumours are

have concluded that they display divergent differentiation of pluri potential cells derived from the uterine stroma. Since neoplastic uterine stroma can produce rhabdomyoblasts in the adult, the possibility that other adult issues may be capable of doing the same cannot be excluded. However, for reasons already given, it is probable that very few, if any, of the extra-uterine rhabdomyomatous tumours arise in this way, the origin of most of them from young still undiffer entiated tissue seems certain

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Liebow A A and Tennant R (1941) Amer J Path 17 1 Lochrane C D (1933) Proc Roy Soc Med 26 1429 Maconie A C (1944) J Larying Otol 59 32 MacCallum P (1933) Austral NZ J Surg 2 296 palatal tumours reported have been in children, the rhabdomyosarcomas of the vagina are almost restricted to early childhood most of those of the prostate and those of the spermatic cord and epiddymis occur in children or adolescents, and so do those of the bladder. Yet the occasional occurrence of pleomorphic celled sarcoma of skeletal muscles in adults with definite stration of their cells makes in impossible to deny that matured muscle fibres may sometimes give origin to tumours. It must be repeated however that mapliastic tumour cells lacking cross strations cannot be identified with certainty as rhabdomyomatous and that most sarcomas in which undoubted cross strations are demonstrable are from youthful subjects.

(2) Structure

Many rhabdomyosarcomas especially those in young children contain undifferentiated myxoma like tissue closely resembling embryonic mescentymer. This applies particularly to the palatal vaginal and prostate tumours the structure of which leaves little room for doubt of their truly embryonic nature. In these sites there occur also similar tumours devoid of recognizable muscle elements and composed solely of myxosarcomatous or embryonic miscentism il tissue.

(3) Sites of origin

It is a striking fact that in spite of the vast bulk of the skeletal muscles of the body undoubted rhabdomyomatous tumours are much rarer in this than in certain special situations where normally no strated muscle is pres nt or where the scanty muscle which is present is only doubtfully the real source of the tumours—vagina, prostate bladder spermatic cord palate. It is of course possible that the palatal tumours spring from the palatal muscles the prostate tumours from the stray strated fibres found in the eapsule of this organ and the viginal tumours from outlying strands of the vaginal or external vesical sphineters. But even so how remarkable that these scraps of muscle should produce far more tumours than all the rest of the voluntary musculature!

From these three sets of facts it seems clear that the usual soutce of rhabdomyo matous tumours is not adult muscular tissue but embryone tissue either immature prospective muscular tissue or indifferent mesenchymal tissue with the potency for abereant differentiation of muscle fibres. That mesenchymal tissues not of rhabdomyoblastic origin can at times undergo such aberrant differentiation is proved by the occasional presence of striated muscle in unusual sites such as the bronchi uterus ureter or spinal theca by its development in embryonic renal and hepatic tumours and by its frequent presence in mixed tumours of the uterus. These pathological ficts show plainly that the capacity to form striated muscle fibres is not restricted to cells derived from the embryonic myotomes but that under appropriate circumstances it appears also in plastic mesenchymal cells of other origins.

The implications already touched on of the development of rhabdomyoblasts in the mixed tumours of the uterus deserve further emphasis. Not only does this show that mesenchimal cells of non muscular origin can re differentiate into myoblasts but also that this change can take place in adult tissue. We have rejected the view that the uterine mixed tumours arise from embryonic rests and

CHAPTER 49

THE TUMOURS OF LYMPHOID TISSUE

Nowhere in pathology has a chaos of names so clouded clear concepts as in the subject of lymphoid tumours. Lymphoma, lymphocytoma, lymphosarcoma lymphoblastoma, follicular lymphadenopathy, lymphate leukaemia lymphod leucosis, leukaemia and aleukaemic lymphadenosis. Hodgkin's disease, Hodgkin s sarcoma lymphadenoma lymphogranuloma leucosarcoma pseudoleukaemia endothelioma, reticulosarcoma, reticulosis reticulo endotheliosis mycosis fing oides—these are some of the names which have been applied to neoplasms of lymphoid tissue and often applied in different senses by different writers. As in so many other fields of pathology, this confusion has resulted largely from failure to recognize frankly certain intrinsic difficulties in the subject and to apply certain general principles in their clucidation. What are these difficulties and these principles?

FACTORS CONFUSING THE NOMENCLATURE OF LYMPHOID TUMOURS

 Confusion regarding the histogenesis and relationships of the components of lymphoid tissue

A great deal of the redundant nomenciature has come from too rigid concepts of the specificity of the several differentiated constituents of lymphoid tissue As long as one believes that lymphoblasts reticular cells, endothelial cells and fibroblasts in this tissue are immutable and distinct species of cells, so long will one imagine corresponding distinctions to exist between the variant types of lymphoid tumours Informed study of the lymphoid tumours however, should soon convince the unbiassed that the components of lymphoid tissue-lymphocytes and reticulo endothelial framework alike-arc derived by divergent differentiation from primitive mesenchymal stem cells the combinations and transformations seen in tumours show clearly that many of them have arisen from and consist of plastic bipotential tissue capable of such divergent differentiation of this will enable us to see the several named types of tumours not as rigidly distinct species but as related variants of a single species and the names we apply will then be used as convenient descriptive labels and not as bones of contention We will cease to be surprised that Hodgkin's disease merges over histogenesis with lymphosarcoma on the one hand and with "reticulosarcoma" on the other

This is the place also to deprecate too great a reliance on supposedly specific reticulin stains. Reticulin is not a specific substance but only a form of collagen found in particular situations and not to be sharply distinguished from ordinary connective tissue fibres either structurally or tinctorially. The distribution and staining properties of collagenous tissues—including 'reticular tissue—in tumours and inflammatory lesions are infinitely variable. My opinion after a considerable experience of special stains for connective tissue and reticulin is that while these often do delineate fairly characteristic pitterns in typical specimens of particular classes of tumours, they are of no value in identifying

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(4) Practical difficulties of micro-diagnosis of early neoplastic changes in lymphoid tissue

The micro-diagnostician has no greater bane than the 'doubtful lymph gland' Early lymphosarcomas, early Hodgkin's disease, mild inflammatory reactions and reticular hyperplasias may be difficult or impossible to distinguish from one another. This is not surprising, for lymphoid tissue varies greatly in structure in its normal or mildly hyperplastic states, its reticulo-endothelial cells proliferate quickly and in diverse ways in response to slight irritants, and many of the lymphoid tumours even when well established mingle intimately with the residual normal tissues. Let us frankly recognize our liability to err here, while striving to learn as much as possible by careful follow-up of all doubtful eases. No pathologist lives long enough to become infallible in this field.

THE HISTOGENETIC KINSHIP OF THE LYMPHOID TUMOURS

Ginsburg has given a good historical summary of the controversy over the relationship of lymphosarcoma and Hodgkin's disease, how at the end of the last century, kundrat, Paltauf, Sternberg and others attempted sharp distinction of the two and how Gibbons, Mallory, Warthin and others later insisted, on the contrary, that they were closely related Mallory (1914) went even further and boldly declared lymphosarcoma lymphotic leukaemia and Hodgkin's disease to be only variants of one kind of tumour, 'malignant lymphoblastoma' Most pathologists and all clinicians, however, continued—and many still continue—to think of these three conditions as distinct and to argue about their relation ships

In 1931, Warthin published a succinct and important paper in which he concluded 'that Hodgkin's disease is a neoplasm and related genetically to the lymphoblastomas, of which both the aleukaemic and leukaemic forms are identical pathologically, and that mycosis fungoides is likewise a neoplasm belonging to the same generic group. The essential differences between these different clinical forms consist in different degrees of differentiation or entidifferentiation, and the organ or tissue primarily involved. Transition forms exist between all of these groups, and one type may be transformed into another." Most recent students of the subject, including myself have reached substantially the same conclusions as Warthin, and have included the relatively rare reticulosariomas and follicular lymphomas in the same family, at opposite ends of the scale as regards malignancy. The whole group is thus seen as an entity 'sarcomas of lymphoid tissue," within which a wide range of structure and behaviour justify, for descriptive and clinical purposes the use of special names for the main variants. But these variants are not distinct species of growths (See Dawson et al., Warren and Picena, Gall and Mallory Herbut et al.)

Complicated pigeon-hole systems of clinical classification of the variants of lymphoid and other haemopoictic tumours, like those of Callender and of Forkner, are to be avoided, because they create a multiplicity of names which their falsely assume the status of entities, even against their creators intentions. The same applies to complicated listopathological sub divisions, like that of Robb Smith, which praiseworthy though it may be as an attempt to clarify a coffused subject, obscures the essential unity of the whole group of lymphoid neoplasms. Many of

tumours of unusual structure or uncertain nature. In my hands reticulin, 'stains have rarely if ever given any useful information which was not equally well obtained by the more usual staining methods. To depend on "reticulin staining for the sub division of lymphoid tumours or to distinguish these from diffusely infiltrating secondary tumours in lymphoid tissue is to set up purely artificial distinctions and to add to the confusion.

(2) Multiple names due to differences of cellular maturity or anaplasia in tumours

Further artificial distinctions are ereated by naming tumours merely according to the degree of differentiation attained by their cells. Thus a tumour composed of highly differentiated lymphoid tissue with follicles is giant follicular lymph one composed mainly of well differentiated lymphocytes but without follocular arrangement is lymphocytoma one composed mainly of immature lymphoeytes is lymphoblastoma one composed of undifferentiated mesenchymal stem cells is syncytial reticulosarcoma. Yet all of these are histogenetically identical growths differing only in their rates of growth and therefore the degrees of differentiation towards that of lymphoid tissue which they attain They are all lymphosarcomas, in that they are malignant mesenchymal tumours with a tendency to differentiate into lymphocytes. To give different members of the group different names merely because of their differing degrees of ecliular anaplasia or maturity is as if one were to attempt to sub-divide skin carcinomas into epidermocytomas epidermoblastomas nnd epithelioblastomas according to their degree of differentiation

A further feature related to the cellular maturity of lymphoid tumours complicates nomenclature—that is the presence or absence of a leuk nemie blood picture it cannot be too strongly insisted that lymphoid leukaemia and lymphosareoma differ only in the quite incidental circumstance of whether or not the malignant lymphocytes enter the circulating blood in demonstrable numbers. Leukaemia is merely an inconstant concomitant of lymphosareoma of interest to the haemat ologist but of no significance in fundamental classification and nomenclature of lymphoid tumours. Once this essential fact is admitted names such as pseudo leukaemia aleukaemia eleukaemia e

cease to eause perplexity and will have only an untique interest

(3) Confusion due to mistaking secondary fumours in lymph nodes for primary ones

This has been a serious source of error in the description and naming of primary lymphoid tumours. Metastate deposits in lymph glands from unsuspected primary careinomas have frequently been mistaken for endotheliomas. Teilieu locytomas and other primary lymph glandular tumours. In 1934. I gave instances of such mistakes ind rejected many earlier reports of endothelioma on this ground. It is to be insisted that when confronted with a lymph nodal tumour the structure of which perplexes and clients differences of opinion from experienced pathologists no final diagnosis should be made until careful necropsy has eveluded the possibility of it being a metastate growth. To accept it as primary and to force it into one or another of our preconceived sub-groups is to commit an error more often than not and so to perpetuate misconceptions of the structure possible within those sub-groups.

often leading ultimately to widespread disease of many lymph nodes with or without involvement of the spleen, and sometimes associated with areas of Hodgkin's structure or terminating in more active sarcomatous growth or leukaemia. The affected glands show abundant well differentiated large follicles with germinal centres, but sometimes with more active diffusely cellular areas like ordinary lymphosarcoma. The disease is to be regarded as a slowly progressive highly differentiated form of lymphosarcomatosis. The average total duration of Gall and Millory's 38 cases was 56 years a longer mean duration than for any other type of malignant lymphoid tumour, more than half the cases survived 5 years and 16 per cent survived 10 years. Males and females were in equal numbers. For the following example of the disease, I am indebted to Dr. C. A. Duncan of Hobart, Tasminia.



Fig 371 -Case II Follicular lymphosarcoma (x 40)

Case II—History.—A man aged 46 had first noticed enlar, sement of lymph glands of years previously. These had slowly increased but general health had remained good Some cough and pain in the chest had developed recently. Extimation showed cervical availary, that and inguinal glands all greatly enlarged some measuring 7 centimetrs admeter discrete hard and mobile also moderate firm splenomegaly Blood examination showed a few nucleated red corpuscles but no other changes leucocyte count was 8 000 Clinical diagnosis. Hodgkin's disease. A lymph gland 3 continuentes in diameter firm and well-encapsulated was exceed for examination. Patient died 4 months later Histology.—Well differentiated lymphoid tissue with many large folicies but with some diffuse areas, and less regular architecture than that of Case I (Fig. 371)

LYMPHOSARCOMA AND LYMPHOCYTIC LEUKAEMIA

Lymphosarcoma means a malignant tumour of lymphoid tissue which is predominantly lymphocytic or lymphoblastic in structure. It includes both lymphocytomas and 'lymphoblastomas', the distinction between which is entirely arbitrary and depends only on the degree of differentiation of the malignant lymphoid cells. Moreover, the least differentiated lymphosarcomas merge

the variants of structure given different names by Robb Smith may be seen in one tumour. What is wanted is not more, but less complexity in our histogenetic concepts. The structural plasticity of lymphoid tissue and its tumours demands the simplest possible nomenclature and avoidance of needless arbitrary distinctions.

However this essential unity of the whole group of primary lymphoid tumours does not call for abolition of broad sub grouping according to the structure and behaviour of its main variants. The sub grouping will continue to have clinical and descriptive value—but it must not cause us to forget the kinship of the subgroups and the existence of tumours of intermediate form between them. We will briefly consider the following sub-groups.

- (a) Follicular lymphoma
- (b) Lymphosarcoma with or without leukaemia,
- (c) Hodgkin s disease,
- (d) Reticulum cell sarcoma

It must be clearly understood that these are main groups only and that while many tumours fall into one or other of them, others show all possible combinations and transitions. These combinations and transitions will cause us perplexity only if we allow the names of our four main sub groups to assume the status of distinct species.

FOLLICULAR LYMPHOMA

Follieular lymphoma means literally a lymphoid tumour in which differ entiation of follicles takes place. In this sense there are two rather distinct groups of eases both of which are rare—(a) a localized benign lymphoma and (b) a multiple malignant form with or without splenomegally

(a) Localized benign lymphoma

This occurs as a slow enlargement often over a period of several years of a single lymph gland usually in the neck and usually in a middle aged or old person. The excised gland which may have attined a size of 5 centimetres or more in diameter is ovoid smoothly encapsulated and on section shows uniform firm, but not hard white tissue in which lymphoid nodules may be discernible by the naked eye. Microscopical examination confirms that the structure is that of well differentiated lymphoid tissue in which large follieles with prominent germinal centires are scattered throughout. While extension to other glands or more active sarecomatous growth or leukaemia may eventually supervene not a few tumours of this kind have been cured by simple enucleation or irradiation. The following cave exemplifies the disease

Case I—A healthy woman aged 46 had a slowly enlarging well-defined lump in the upper part of her neck for 8 years. It was thought to be a salivary lumour and was excised it was an encessful substitute of uniform soft white insue.

Illustracy—Well-differentiated lymphoid tissue containing large follicles with germand centres throughout.

(b) Multiple follicular lymphoma or lymphosarcoma

This has been well described by Symmers (1938 and 1942) It presents slow enlargement of one or more groups of glands with extension to other glands,

clinically less obtrusive abdominal disease, just as it is with some abdominal caremomas. In my 34 necropsies the abdominal lymph glands were those most heavily involved and were considered to be the primary site of disease, in 22 cases

The axillary or inguinal lymph glands, the tonsil pharynx, intestinal lymphoid tissue or spleen are all occasional primary sites of lymphosareoma. It must be remembered, however, that tonsiliar or pharyngeal carcinomas of anaplastic

lympho cpithelial' type (q v) have often been mistaken for lymphosarcomas, and that it is often difficult to be sure of the primary splenie or intestinal origin of an abdominal lymphosarcoma because in most cases by the time the tumour is seen many neighbouring lymph glands also are affected. Good accounts of primary intestinal lymphosarcomas include those of Jopson and White, Libman, Graves, Ullman and Abeshouse, Simpson Smith, and Webster



Fig 372 -Case III Lymphosarcoma invading lung (x 80)

The following case presented an extensive lymphosareoma of lung tissue and only slight involvement of peribronehral lymph glands presumably therefore the tumour arose from the bronchial lymphoid tissue

Case III—History—A man aged 57 had had 9 attacks of 'pneumona' in the last 3 years skeagams showed large opacity in right upper lung field Lobectomy was performed by Mr C J O Brown The specumes showed a large mass of diffuse white agrowth 8 custometres in main diameter extending from hilum of lobe to its outer surface where pleura was thickened and adherent Histobecy (Figs 372-34)—Weld differentiated imphocytic san.oma mainly diffuse but with trabeculae of hydine collagenous tissue 'with a few poorly differentiated follicles. The tumour had completely obliterated a Lymfung tissue in most places at its periphery it invaded this tissue was the inter alweidar in man and perivascular and penbronchial tissues. Carbonized hilar and peribronchial septiments of tumour.

rbitraneral survey of the literature it seems not unlikely that the distribution of a cellsy sites of lymphosarcoma is nearly in proportion to the relative bulk tion of prima

insensibly with the syncytial reticulosarcomas, as will be readily appreciated from almost any of the recent accounts of the latter

Lymphocytic leukacmia means the demonstrable presence of malignant lymphocytes or lymphoblasts in the circulating blood. It is not a species of disease but merely a concomitant of some lymphoblastic tumours a concomitant the frequency of which is not only readily understood but was clearly to have been expected, from the natural mode of formation and mobilisation of lymphocytes. Leukacmia may appear during the progress of previously aleukacmic cases. In Gall and Mallory's series leukacmia was found in 48 per cent of cases of lymphoblastoma and 38 per cent of cases of lymphoblastoma.

Except for the demonstrable presence or absence of malignant cells in the circulating blood there are no differences between lymphosarcoma and lymphatic leukacmia in either gross or microscopic pathology. Every possible combination and variation in the distribution of lesions is encountered—large localized lymphosarcomatous tumours with or without leukacmia. widespread involvement of many or all of the lymph nodes and other lymphoid tissues of the body constituting generalized. lymphosarcomatous, with or without kukacmia, and with any of these there may occur in other organs either well defined metastases or diffuse metastatic infiltrations. From microscopical examination of affected lymph nodes alone, it is impossible to distinguish leukacmie from non leukacmie eases.

(1) Age and sex incidence

(a) Age

Although not rare in youth even in infancy lymphosarcoma is predominantly a disease of middle and old age. In Gall and Mallory a series the mean age at onset of 76 cases of lymphoblastoma was 40 years and in 51 per cent of the cases the onset was at ages over 40 and of 118 cases of lymphocytoma the mean age at onset was 44 and 65 per cent began at ages over 40 years. The ages of my 34 necropsy cases of lymphosarcoma ranged from 14 to 78 18 (i.e. more than one half of them) were over 50 years old and the mean age was 52 years.

(b) Sex

As in all other sub-groups of lymphoid tumours males outnumber females the ratio being 2 or 3 to 1 in most series. My 34 necropsies were on 25 males and 9 females.

(2) Site of origin

The site of origin of the tumours is not always clear. In many of those presenting as cases of leukaemia or of generalized lymphosurcomatosis the initial site of origin cannot be specified or can only be guessed at. In other cases a large tumour of a particular region suggests but does not always prove that the tumour began in this region.

The cervical abdominal and mediastinal lymph nodes are the commonest initial sites usually given in that order of frequency. The predominance of cervical growths however may be more apparent than real because these are sooner noticed than those of the abdominal or thoracie glands and because massive disease of the cervical glands may sometimes be secondary to earlier but

(b) Sex

There is a decided predominance of males over females in the ratio of 2 6 to 1 in Galf and Malfory's series My biopsy and necropsy records concern 38 males and 11 females

(c) Site

It is often strited that the cervical lymph glands are those most often first affected, but doubts like those already expressed regarding the primary sites of lymphosarcomas apply to many cases of Hodgkin's disease also Cases of supposedly primary splenic or intestinal Hodgkin s disease" also are seldom indubitable these are usually only clinically primary in that splenomegaly or intestinal symptoms constituted the first signs of disease

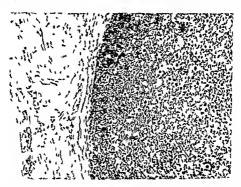


Fig. 377—Cortical zone of a cervical lymph gland affected by early Hodgkin's disease in a man aged 19 showing loss of follocular pattern and many large multiplying reticular cells \$\times\$120\$)

(2) Structure and histogenesis

The characteristic but rather variable structure of Hodgkin's tissue is well described and depicted by Pullinger In the early stages (Figs 377, 378), there is gradual loss of normal nodular architecture of the lymphod tissue, the lymphocytes and their precursors tending to form instead diffuse sheets mingled with prolifer iting reticulum cells, this diffused lymphod tissue contains few or many large conspicuous rounded or irregular cells measuring from 20 μ to 100 μ or more in diameter, containing single or multiple nuclei numbering up to 8 or more per cell, and showing many mitoses, cosinophil neutrophil and basophil granulocytes and plasma cells in variable numbers mingle diffusely or patchily with the proliferating ussue. In the later stages plentful fibrous tissue develops first in bands separating lobules of the more cellular Hodgkin s tissue,

of lymphoid tissue in the different regions of the body, and that no particular part of the lymphatic system is disproportionately liable to neoplasia. The question

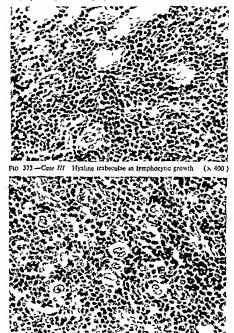


Fig. 374—Case III Large undifferentiated cells resembling those of Hodgkin's disease in himphocytic growth (× 400)

of multicentric origin is discussed below along with that of metastasis

(3) Structure

It is unnecessary to repeat in detail the well-known features of

of Hodgkin's disease (Warthin, Gill and Mallory, Gill and McCall), and by the presence in acute Hodgkin's disease of areas of tissue indistinguishable from large celled lymphoblastomas Lesions designated "Hodgkin's sarcoma" may contain treas of such tissue, or of tissue identical with that of syncytial reticulosarcoma, or of both

The fibrosis of old Hodgkin's lesions may not be merely the result of stromal reaction, but may be a specific feature of the tumour tissue. Since the proliferating tumour cells are reticular, and since reticular proliferation in lymphoid tissue often participates in fibrosis, we might expect that a slowly growing Hodgkin's lesion should become densely fibrous, just as a slowly growing fibrosarcoma may Thus the chronic Hodgkin's lesion, in so far as it is a fibrosing lesion is a genuinely fibrifying tumour-a kind of fibrosarcoma of lymphoid tissue

In my view then Hodgkin's disease is a tumour of primitive reticular cells in which divergent differentiation of both lymphoid and fibro reticular elements takes place. These elements are found in varying proportions and varying degrees of differentiation. When the growth is highly undifferentiated or anaplastic it becomes indistinguishable from, and indeed identical with, the undifferentiated stem cell or syncytial reticulos recoma Through Hodgkin's disease, all sarcomas

of lymph glands are related

The view that Hodgkin's tissue has myeloid affinities or potentialities seems to me to rest on insecure bases These are three, namely, (a) the frequent admitture of granulocytes in the tissue (b) a supposed resemblance of Hodgkin's giant cells to megal aryocytes, and (c) the very occasional coexistence of Hodgkin's disease and myeloid leukaemin As to (a), I doubt if any modern pathologist would seriously sustain the view that the granulocytes in Hodgkin's tissue are genetically related to and derived from that tissue they are very variable in kind, number and distribution and have all the appearance of being immigrant reactionary leucocytes such as occur in many a carcinoma As to (b), Medlar (1931), and Symmers (1938 and 1942) are as far as I know the only modern exponents of the view that the multinucleated cells of Hodgkin's disease are indeed bone marrow megakaryocytes, a view for which comparison of the two kinds of cells gives no support As to (c), the coexistence of myeloid leukaemia and Hodgkin's disease has been reported so rarely (references by Forkner and by Gill and McCall), that the association may well be no more than fortuitous, and it must not be forgotten that myeloid reaction with or without eosinophilia, in cases of Hodgkin's disease with involvement of bones, might be mistaken for leukaemia in view, then, of the very dubious relationship of any of the proper constituents of Hodgkin's tissue to those of bone marrow, it would be wise to avoid Pullinger's and Robb-Smith's name fibro myeloid retrialing only 'reticular proliferation and contributing nothing to our understant. lessons to which it has been applied

The eponyms bestowed on the large multinucleated craberg or 'Reed" or disease call for comment. These are usually called St. lescription in 1898 and 'Sternberg Reed' cells, because of Carl Sternberg Reed's description in 1902. But in 1878 as sympostamed several contributions in which these cells were referred to Thus Greed.

Thus Greek

later more extensively replacing this tissue and sometimes converting almost the whole of an affected gland into a hyalinized fibrous mass — Small groups of large or multinucleated cells often persist here and there in densely fibrous areas and eosinophil leucocytes also are found in them

Most workers agree that the essential proliferating elements in Hodgkin s tissue are the large and multinucleated cells—the so called "Sternberg Reed giant cells —and that these are neoplastic reticulum cells The granulocytes and plasma cells in Hodgkin s tissue appear clearly to be only recitionary elements similar to those seen in many other kinds of tumours. The two remaining components namely, the lymphoid cells and the fibro reticular tissue, require special consideration

In Hodgkin's lesions in lymphoid tissue itself, it is impossible to decide whether the plentiful lymphocytes and lymphoblasts which are present are essential tumour

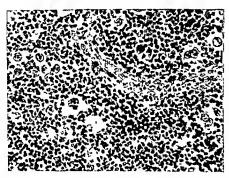


Fig 378 -Detail of Fig 377 (> 300)

cells or are merely residues of the original tissue. But in secondary deposits of Hodgkin's tissue in the liver, lungs skin or other non-lymphoid structures, lymphoid cells are again present and are often plentiful thus appearing to be an integral part of the lesions. We must conclude then either that the neoplastic proliferation itself produces these cells or that lymphocytes are attracted into and multiply in it wherever it occurs—as in lympho epitheliomas. Of these two alternatives there is atrong I think conclusive evidence in favour of the former. In Hodgkin's lesions it is impossible to distinguish with precision between immature lymphoid and immature reticular cells and the varieties of size and shape of the cells encountered strongly suggest that all of these are tumour cells differentiating from a stem-cell precursor in two divergent directions. This concept is supported by the not infrequent occurrence of lymphocytic leukaemia in cases

by a large hard mass of growth adherent to stemum ribs and clavicles invading and partly replacing upper lobe of right lung and surrounding and invading superior ven acra? Right man bronchus was surrounded by growth in bronchus lithyphig lands and its mucosa showed a nodular ulcrated plaque 2.5 centimetres in diameter. Both lungs contained also multiple, discrete reaso for white growth the largest 5 centimetres in diameter and nodules and plaques of growth were present in right pleural cavity. Thyroid was invaded from cervical glands and largely replaced by growth. Liver contained only one small white nodule. Spleen and almentary canal normal and no deposits found on section of skull sterum and vertebrae. Necropsy diagnosis carcinomis of right bronchus with extensive lymphatic metastases. Histology.—Typical chronic Hodgkin is disease with multimucleated cells much dense fibrosis and many cosinophil leucocytes. (Comment—The case is notable not only because of the bronchial lesion but also because of the presence of a large mediastinal tumour and gross in wasion of a mini ven.)

Case VII - Female aged 39 Symptoms - Clinical and radiographic signs of large anterior megiastinal tumour Accropri-Hard white irregular nodular tumour 10 centimetres in main diameter by in upper anterior mediastinum enveloped the sortic arch and adhered to base of heart and to vertebrae and first rib. Sections showed pen pheral parts of the growth to include enlarged coalescing lymph glands. Its central parts contained many areas of suppuration ramifying from an area of necrotic ulceration 2 centimetres in diameter in lumen of left bronchus Lift lung was collapsed and showed patchy pneumonia. Right hilar lymph glands contained small deposits of firm white growth. All other groups of glands and other viscera including spleen appeared normal Histology-Bulk of growth Necropsy diagnosis infected mediastinal tumour consists of dense hyaline fibrous tissue with patches of lymphocytes plasma cells and cosmophil granulocytes but parts near root of lung and in bronchial wall show typical active Hodgkin's disease

Case VIII—Male aged 75 Simptoms—Dubility and disphagis for 4 months and enlarged cervical and availary glands both sides clinical diagnosis. 7 gastric carrinoms Necropy—Moderate enlargement of cervical availary all mediantinal and retropentional lymph glands those of right availa coalescing to form an irregular infiltrating mass 8 centimeters in diameter adherent to ribs and muscles and showing much yellow degeneration. Hitum of left lung contained an irregular friable mass surrounding main bronchus and ulcerating into it at several places but not invading lung itsue. Spleen not enlarged but studded with firm white nodules. Other organs all appeared normal Necropia diagnosis. 9 Hodgkin is desease 7 bronchusi carcinoma. Hituboey—Cellular Hodgkin 5 disease—Hodgkin s sarrouma—with many large and multimucleated cells with many mitoses. Availary mass shows unusually extensive necrosis.

(b) Hodgkin's deposits in bones

These are present in the majority of fatal cases, and would perhaps be found in nearly all if searched for (Uchlinger, Steiner) While bones may be invaded directly from neighbouring lymph nodes (as in Uchlinger's Figs 6 8 and 9) most of the skeletal lesions are clearly blood home metastatic deposits in red bone marrow. They have a distribution similar to that of other kinds of metastatic growths the bones most frequently affected being the vertebrae pelus sternum ribs, and proximal end of the femur. They appear usually as multiple discrete or confluent areas of white tissue not to be distinguished by the naked eye from other metastatic tumours. They are often unsuspected clinically but may lead to radiographically obvious lessions, to timefaction of the bone or to pathological fracture. Weigall and Detrick reported a remarkable case in which vertebral lesions gave the first signs of disease and simulated tuberculous carries and in which a circumscribed deposit caused prominent expansion of the head of a

glands of Hodgkin s disease.— In the early stages there was some general enlargement of the glands the fibrous stroma appeared coarser, and there were a large number of multinucleated cells adherent to the trabeculae, well seen on washing away the lymph cells. These multinucleated cells containing from four to eight or twelve nuclei, were often collected in elusters in the parts of the gland especially where the fibrous change was progressing." Greenfield clearly depicted these cells and in the spleen also he saw 'cells of various sizes massed together, a good many large multinucleated cells being annogast them." At the same time, Sutton also saw in Hodgkin's lymph glands many large and very con spicuous cells of round or oval form, and having a considerable amount of protoplasm around the nuclei, and in the spleen "large cells, many of them polynucleated, similar to those seen in the lymphatic glands. Coupland too, referred to numerous large nucleated cells occurring mingled with the smaller lymphoid cells." In the same year as Dorothy Reed's paper. Andrews also independently described the large cells of Hodgkin's disease. Hence if Dorothy Reed s name is to be retained eponymically, we shall have to employ a compound title including the names of at least 6 writers.

(3) Spread, metastasis, and the question of multifocal origin

The discussion already given regarding the parts played by metastasis and systemic origin in the extension of lymphosarcomas applies mutatis mutandis to Hodgkin's disease While study of early Hodgkin's changes in lymph nodes makes it clear that in some cases the disease arises multifocally or diffusely within a particular territory of lymphoid tissue it is equally clear that metastatic spread from node to node or by the blood stream plays an important part in its dissemina tion Small lymphatics and veins are often to be found invaded by Hodgkin's tissue and arteries and large veins also are invaded (see Uehlinger's Figs 18 and 19 and Case VI below) Even if one were prepared to suppose that all lesions in lymphoid and other haemopoietic tissue were multiple autochthonous foei and never metastases, this could searcely apply to circumscribed lesions in the lungs skin nervous system and other non haemopoietie organs. In the liver, spleen and bone marrow also while in some cases Hodgkin s infiltrations are diffuse or only indefinitely nodular in other cases the deposits form well defined white masses set in organs showing little or no evidence of diffuse involvement just like any other metastatic growths

(a) Involvement of the lungs and mediastinum

This deserves special comment. It may occur as scattered metastatic deposits in the lung substance or as extensions from disease of the hilar or mediastinal lymph glands or as a large mediastinal tumour. Hilar lesions may surround and invade the main bronchi and so may be indistinguishable grossly from bronchial careinoma as in the following cases:

Case II—History—A man aged 2t developed a mass in lower left part of neck further masses appeared later in other parts of neck and both axillae. These were diagnosed clinically as Hodgkin's disease and treated by X rays and arsenicals with benefit. Recurrences however appeared including a large mediastinal mass seen in skiagrams and the man died at the age of 25. Necropsy—Hard enlargement of lymph gliands in all parts of body partly discrete partly diffuse and confluent. Antenor mediastinam occupied

The only tumours to which the term "reticulosarcoma 'is strictly applicable are those in which differentiation of reticular tissue type is distinct and predominant. These tumours used to be called 'endothehomas' of lymph glands, a diagnosis however, which was often erroneously made also in cases of metastatic carcinoma. It cannot be too strongly insisted that complete and careful neuropsy study is often the only means of establishing—or refuting—the primary nature of an anaplastic tumour of uncertain nature in a lymph gland. Of Roulet's much quoted paper (1930) it is to be noted that in many of his cases of "Retothelsarkom" no necropsies were performed, and that some of his figures (e.g. Figs. 7 and 8) might well be diffuse carcinoma. Until this source of confusion is climinated, it will not be possible to make a rehable analysis of the properties of the true reticulo sarcomas of lymphoid tissue. Most of these tumours have occurred in adult males have consisted of spindle celled or pleomorphic celled tissue, and have shown a tendency to spread from gland to gland as well as by the blood stream.

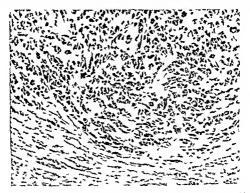


Fig. 379—Case X. Reticulosarcoma of epitrochlear lymph gland. (< 120)

I have performed necropsies on three cases in which the final diagnosis was reticulum cell sarcoma of lymph glands, in two cases there were also features resembling Hodgkin's disease. These cases were briefly as follows

Case Y—(Reported in 1934 p. 437 No. 57) Male aged 66 Spindle-ceiled sar-oma of epitrochlear lymph gland with extension to axillary and supraclavicular glands and metastases in lung, myocardum adrenals pancreas mucosa of ileum and colon pen toneum skull and skin (Fig. 379)

Cuse \(\frac{1}{2}\)—Male aged 43 \(\frac{5}{2}\) imptoms—Enlarging mass recently noticed in left side of neck was excised and found to consist of an enlarged lymph gland replaced by soft white tissue Microscopically this consisted of undifferentiated cellular polyhedral celled growth with many microses of uncertain nature, possibly primary sarcoma possibly secondary anaplastic carcinoma \(\frac{Dep \text{A}}{2}\) ray therapy was applied to neck and there

rib Uchlinger described several examples of vertebral collapse and paraplegia from Hodgkin's disease, and also an unusual sternal deposit with vertical spicules of periosteal new bone radiographically misdiagnosed as 'osteogenic sarcom.' The following case was unusual both because bone lesions caused the first symptoms of the disease and because of the patient's age.

Case IX—(From Dr Basil Jones of Horsham Victoria) History—Female child aged 4 years had had pain and limitation of movement of right shoulder for 6 months On examination the only other abnormalities were moderate enlargement of right avillary lymph glands and doubtfully palpable spleen. Skia rams showed an area of decalcification of the humerus 4 centimetres long involving the miner aspect of the shaft just below the head and extending into the head and epiphysis. Histology—Enlarged gland removed from avilla showed typical Hodgkin s disease with fibrosis many multinucleated cells and many consophil leucocytes.

(4) Gordon's test

Gordon's discovery (1932) that intracerebral inoculation of rabbits with Hodgkin's tissue usually produces a characteristic encephalitis but that tissue from other lesions of lymph nodes or from normal nodes rarely does so has been repeatedly confirmed. Positive results have been obtained in three quarters of the cases of Hodgkin's disease tested (Steiner) That the test is not specific, however is shown by the positive results obtained with normal bone marrow, spleen and occasionally some other tissues. That it is probably due not to a virus but to some chemical substance or enzyme is shown not only by these positive results with normal tissues but also by the fact that attempts to transfer the encephalitis from rabbit to rabbit have failed Edward Robb Smith and Turner et al have advanced strong evidence that the agent responsible for Gordon's test resides in the granular leucocytes, especially the eosinophils, and that it is by virtue of the presence of these cells in considerable numbers in Hodgkin's lymph nodes that these give a positive result. Robb Smith obtained positive results from eosinophil infiltrated lymph nodes in trypanosomiasis and idiopathic cosmophilia

RETICULUM CELL SARCOMA

We have already concluded that Hodgkin's disease in so far as it is a malignant tumour of the reticulum cells of lymphoid tissue is a form of reticulum cell sarcoma This term is, however, more strictly applied to tumours in which the predominant or only line of differentiation of the neoplastic cells is towards reticular connective tissue ie to fibrifying tumours allied to fibrosarcomas It has also been extended to include the undifferentiated or anaplastic ' syneytial reticulosarcomas' which however are not sharply separable from other anaplastic sarcomas of lymphoid tissue— Hodgkin's sarcomas and primitive lymphoblastomas. As regards all of these anaplastic growths indeed it is necessary to recall-what should be obvious-that their very anaplasia renders attempts to sub-divide them inadvisable. Structurally they can be identified no more specifically than as anaplastic sarcomas. In my opinion, Hodgkin's diffuse syncytral reticulosarcoma', trabecular syncytial reticulosar sarcoma dictosyncytial reticulosarcoma, and 'lymphoblastic reticulosarcoma coma are not separable but are only arbitrary names for variants of the same thing

While there is little doubt that the growths in these three cases were primary tumours of lymph glands. I confess to some indecision as to their most appropriate names in spite of careful histological study. They were provisionally called reticulosarcomas, but the tumour of Case X might equally well be called simply "spindle celled sarcoma" while those of Cases XI and XII might equally well be called atypical Hodgkin's disease. "From the cases recorded by others as reticulosarcomas. I suspect that similar indecision might well have obtained in some of these though not admitted by the authors.

Kaposi s sarcoma

This peculiar disease may be conveniently mentioned here. It has been studied mainly by dermatologists and has been variously regarded as a granuloma round celled sarcoma angiosarcoma, haemangio endothelioma reticulosarcoma and a peculiar form of fibrosarcoma (Symmers 1941) While the long duration of the disease often many years the great predominance of males the high proportion of Jewish patients and the appearance and course of the skin lesions certainly suggest a pathological entity the histo pathology of recorded cases has been very variable and non distinctive. The only case which I have personally studied, in which the lesions resembled those commonly described as Kaposi s disease, was Case XII above and I feel confident that this was one of fibrifying reticulo sarcoma of lymph glands with plentiful admixed lymphocytes. This experience leads me to wonder if Kaposi s disease may not be one of the many variants of lymphoid tumours with prominent skin lesions related to those of Hodgkin's disease and mycosis fungoides Such a histogenesis would not exclude Symmets's view that it is a peculiar form of fibrosarcoma, for fibrosing Hodgkin's disease and reticulosarcomas also are peculiar forms of fibrosarcoma Additional careful necropsy studies of cases of this disease are needed

TUMOURS OF LYMPHOID TISSUE IN ANIMALS

Leukaemic and non leukaemic lymphoblastomas are amongst the commonest tumours of many species of animals. According to Feldman, they account for about one third of malignant growths in cattle and pigs and 15 per cent of those in sheep, they are common also in dogs, mice rats and birds, and rather less common in cats, horses and rabbits (See also Englebreth Holm) Stasney and Feldman made a particularly thorough study of a case of lymphocytic leukaemia in a calf Of the many papers on lymphoid tumours and leukaemias in mice those of Furth et al (1933 and 1935) McDowell McDowell and Richter, and Potter et al are valuable sources of reference Lymphoid tumours in animals have been variously designated by the same names as the human ones-lympho sarcoma lymphatic leukaemia Hodgkin's disease etc-and it is clear from the animal tumours as from the human that these are but variants of a single group of tumours As both Rolleston and Feldman have pointed out the propriety of the term Hodgkin's disease" in reference to most animal tumours is questionable, the histology of the lesions has seldom been so characteristic as to prove its identity with the human lesion. However Stalker et al have de scribed an acceptable example of Hodgkin's disease in a dog Most lymphoid growths in animals are lymphosarcomas with or without leukaemia

was no recurrence of tumour Patient died. 4 months later from acute right lobat pneumonia Necropsy—Several lower cervical lymph glands were slightly enlarged but did not appear diseased thoracic and abdominal glands all appeared normal Except for pneumonia all viscera including all cramo-cervical structures were normal Histology—Some cervical Jymph glands are replaced by fibrous and cellular tissue containing many large polyhedral cells some of which are in mitosis there are also many plasma cells but no eosinophils. Some of the non-enlarged mediastinal glands show small patches of smular tissue with a few cosinophils more closely respenbling Hodgkins disease.

Case XII - Female aged 26 Symptoms - Emaciation recurrent pyrexia and persistent skin eruption diagnosed as pemphigus Necropsy-Lungs contained scattered areas of firm grey or haemorthagic tissue hilar glands were enlarged by similar growth Liver contained many small scattered ill-defined areas of soft white tissue portal glands were greatly enlarged by firm white growth Spleen contained many small white nodules Retroperitoneal and mesenteric lymph glands enlarged and haemorrhagic cervical glands not enlarged but similarly affected inguinal and axillary glands normal Mucosa of stomach and small intestine contained multiple firm white or haemorrhagic nodules up to 1 centimetre in diameter many with central ulceration. Skin showed extensive but patchy infiltration by white or haemorrhagic tissue. Skull contained several small ill-defined areas of soft tissue involving dura. Other bones and viscera normal Necropsy diagnosis abdominal Hodekin's disease Histology (Fig. 380)-Affected lymph glands and deposits in liver lungs intestine spleen and skin show mingled fibro sarcomatous and polyhedral-celled growth with many mitoses accompanied by many lymphocytes and monocytes but no eosinophil leucocytes The tissue contains plentiful small blood vessels areas of haemorrhagic necrosis are common Digenosis-Though not typical of any the tumour shows similarities to Hodekin a disease to fibrosine reticulosarcoma and to kaposi s haemorrhagic sarcoma. It was classified as a primary reticulosarcoma of the upper abdominal lymph glands with metastases to other parts

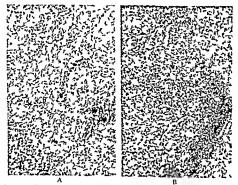


Fig. 380—Case VII Diffuse fibrosing reticulosarcoma with admixed lymphocytes A = from lymph gland B = from liver (x 100)

lymphoid tissue as related variants of one disease. The names used for the prin cipal variants have descriptive and clinical value but do not denote distinct pathological entities Follicular lymphoma is the least malignant, best differ entiated variant of the group, with a structure approaching that of normal lymphoid tissue Lymphosarcomas show predominant differentiation of neoplastic lympho cytes or lymphoblasts Lymphatic leukaemia is lymphosarcoma with a circulating metastasis Hodgkin s disease shows differentiation of both lymphoid cells and reticular elements, the latter often fibrifying Reticulosarcoma is a name best reserved for tumours showing predominant reticular (i.e. fibrifying) tendencies, it is better not to apply it to anaplastic syncytial growths devoid of differentiation

My costs fungoides is only a form of skin lesion of one of the foregoing variants,

perhaps the same applies to some cases of Kaposi s disease"

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As Furth and his co workers have insisted, the pathology of animal tumours closely parallels that of the human ones in almost every respect, and there is no doubt that the disease is essentially the same in all species of mammals. It is however, doubtful whether fowl leukaemia and other avian 'leucoses are analogous to the mammalian diseases. The bird lesions differ in some respects from the mammalian ones and the presence in them of a filterable causative agent also makes them peculiar—just as the filterable avian sarcomas typified by Rous s tumour are peculiar and doubtfully comparable with mammalian sarcomas. As Furth and his co workers have shown the transfer of mouse leukaemia from one animal to another is possible only by the transfer of living intact leukaemia cells and not by injured cells or cell free extracts. Furth and Kahn found that a single intact leukaemic cell sufficed for the transfer of leukaemia from one mouse to another.

Rudduck and I in our necropsies on dogs frequently observed in the spleen a lesion which we could not find adequately described in the literature and which has all the appearances of a lymphoid tumour. This consists of single or multiple, fairly well defined but not sharply circumscribed nodular growths usually I to 3 centimetres in diameter but sometimes larger composed of white tissue mottled by haemorrhage and microscopically consisting of lymphoid tissue aggregated indefinitely in nodules and intervening strands of congested haemorrhagic or pigmented reticular tissue showing some fibrosis and often containing multi-indefinitely in nodules and intervening strands of congested haemorrhagic or pigmented reticular tissue showing some fibrosis and often containing multi-indefinitely in nodules and without evidence of lymphoid tumours elsewhere. The possibility of the growths being infective lesions was not overlooked but careful search of Giemsa stained and Gram stained sections regularly failed to reveal any bacteria and guinea pig inoculations gave negative results. It seems possible, then that these lesions constitute a special variety of relatively benign localized lymphosarcoma or lymphoma of the dog s spleen.

CAUSATION OF TUMOURS OF LYMPHOID TISSUE

So far there is very little substantial evidence either human or experimental pointing to the cuisative agents of lymphoid tumours. Leukaemias developing in persons exposed to benzol or to X rays are usually of the mysloid variety (see Chapter 51). lymphocytic leukaemias in such persons (e.g. those reported by Falconer and by Tarcev cited by Hueper) are so rare that the occupational association is probably only fortuitous. Leukaemiod reactions are observed in animals treated with carcinogenic hydrocarbons, and these substances also cause an increased incidence of lymphoid tumours or leukaemia in strains of mice prone to these diseases (see Chapter 4) but there is no evidence that occupational exposure to carcinogenic hydrocarbons increases the risks of leukaemia or lympho sarcoma in man. However, more thorough inquiry into the past habits and occupations of the victims of these complaints is needed and may eventually discover some of the responsible agents. The marked predominance of males certainly suggests that occupational factors may well be concerned.

CONCLUSION

I join Warthin, Ginsburg Herbut et al and others who regard all tumours of

CHAPTER 50

PLASMOCYTOMAS AND MYELOMATOSIS

TUMOURS consisting of plasma cells are of the following three kinds

Plasma cell myelomatosis

Solitary plasmocytoma of bone

Primary plasmocytoma of soft tissues

Although in a minority of cases of multiple myelomatosis the tumour cells are not distinctly plasma cells and have received other designations in most cases the tumours plainly consist of plasma cells and the disease as a whole is best considered in this context. To the debate regarding the histogenesis of plasma cells, the study of plasma cell tumours has a contribution of value to make

MULTIPLE MYELOMATOSIS

(1) Personally studied cases

The following cases exemplify the main clinical and pathological features of the disease

Case I—Female aged 48 Histori—Recent pain in back, of sudden onset skiagrams showed multiple decalcified areas in vertebrae. 7 myelomatosis ? metaviatic growths' no Bence Jones protein found in urine. Necropsy showed many soft greight tumours in bone marrow of skull vertebrae ribs and pelvis with partial collapse of several vertebrae and pathological Iractures—some healed—of ribs. No tumours in viscera. Histologi—Typical cellular plasma-cell growths with some multimuleated cells. Viscera clear

Case II — Male aged 42 Hastery — After extraction of teeth bleeding persisted and proved fatal 18 days later Necrops; showed many rounded pale soft growths up to 1 continuere in diameter, in vertebrae stemum ribs and pelvis but none occura in femur or skull. No tumours in viscera Hasterogy — Growths consist of typical well differentiated plasma cells some multinucleated [Fig. 381]

Case III—Male aged S8 Itstoy—Pan in back and loss of weight for some monhs test meal showed achienhydria clinical diagnosis carcinomatosis probably from pinning in stomach. Albuminutin by ward tests Nevroyn—Many small rounded soft greyish tumours present in all vertebrae robs sternum clavicles pelvis and femora with partial collapse of several vertebrae. No tumours in skull or in viscest Itstology—Typical plasma-cell tumours with some multinucleated cells. Viscera clear kidneys show patchy calcification within the tubules.

Case IV—Male aged 81 History—Severe pains in shoulders and left arm for some months. Extensive destructive lesson of the seventh cervical vertebra seen in skuagams? myeloma? metastatic growth hecropsy—Lower two cervical vertebrae largely replaced by soft brownish tissue a few discrete soft tumours present in other vertebrae.

fusiform enlargement of several ribs by growth no tumours found in sternum pelus femora or skull Right fobe of thyroid enlarged by an irregular cystic mass which was thought to be possible primary carcinoma with metastases in bones. Histolog.—Typical plasma-cell myelomatosis.

piasma-cell myelomatosis

Case 1 — Femule aged 64 Hustors — Paints in chest and loin for 2 months, more recent left facial oculomotor paralysis and paresis of limbs. Ward tests albumuura constantly present Clinical diagnosis. Landry's paralysis. Necrops—Skull

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or mushroom shaped masses projecting from bone surfaces. Pelvis ribs and femora contained scattered growths several of the ribs with projecting nodular or flusiform masses and pathological fractures. Viscera contained no tumours. Histologi—Tumours consisted of masses of rounded cells of undetermined kind with eccentric spherical or ovoid nuclei resembling myeloblasts or lymphoblasts more than plasma cells. Some multinucleated cells were present and some areas showed much fibrous tissue mingled with the round celled growth.

Case VII—(Reported 1930) Female aged 59 with chinically diagnosed myelomatosis and Bence Jones proteosuria. Multiple but not numerious large tumous in everal parts of skeleton including skull a nb manubrum sterm acromon a metacarpal clavicle humerus sichium femur itbia calcaneus talus and two metatarsals. Patho olgical fractures with sound union and good response of individual tumous to radium or \(\lambda \) rays were notable features. Histology—(biopsy from rib) cellular growth composed of round cells of undetermined kind unlike plasma cells and more like myeloblasts or lymphoblasts multimucleated cells present.

(2) Incidence

(a) Frequency

Myelomatosis is not a rare disease in various series it constitutes from 3 to 25 per cent of all primary malignant timours of bones Because of diagnostic errors, it is impossible to estimate its frequency accurately, not a few early cases escape clinical detection and are disclosed only at necropsy (e.g. Cases II III V and VI above) while in other cases the bone lesions are discovered radiographically but distinction from metastatic growths is difficult or impossible (e.g., Cases I and IV above) Conversely, metastatic growths in bones may be mistaken radio graphically for the lesions of myelomatosis (Cosin)

(b) Age and sex

Three-quarters of the cases occur between the ages of 40 and 70 the mean age is in the sixth decade and the disease is very rare under 30 (Geschickter and Copeland Batts) Men are affected about twice as frequently as women

(3) Distribution and appearance of the tumours in the skeleton

By radiographic examination, Batts found evidence of tumours in the various bones in the following percentages of cases—skull 73 spine 70 ribs 68 pelvis 63 femur 48 humerus 43, shoulder girdli. 40 per cent and the bones of the peripheral parts of the limbs only occasionally. The vertebrae and ribs contained growths in all 6 of my necropsy cases and the pelvis in all but one case, but in 3 cases the skull contained no tumours obvious to the naked eye. The sternum frequently contains tumours. My Case VII was unusual in showing multiple large growths in the bones of the feet. Estimates of the frequency of involvement of various bones based on radiographic or routine necropsy examinations are of course underestimates—not only because such examinations are rarely complete but also because diffuse myelomatous change as in Cappell's and Churg and Gordon's cases might easily escape naked eye or radiographic detection.

The tumours appear as soft sometimes almost fluid grey, pink or red growths replacing the bone marrow and accompanied by absorption of the bone trabeculae. They are usually well defined and nearly spherical, and produce well demarcated.

certebrae ribs sterium and pelvis contained many large soft growths one of these extensively invaded dura over left optic foramen and cavernous simus region—several vertebras showed partial collapse and large paravertebral masses of growth—Multiple small white tumour nodules present in lungs here spleen kidneys panerers hyprod and mucous membranes of stomach and small intertime the largest being in the gastne

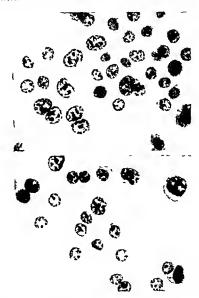


Fig. 381 -Case II Smear of myeloma plasma cells including some with two nuclei. (> 1 000)

mucosa and measuring 2 centimetres in diameter. Histology—In all situations tumours consisted of typical plasma cells with many mutoses and some multinucleated cells. Liver in addition to visible tumour nodules showed diffuse plasma-cell infiltration of portial tracts: and splene pulp contained many plasma cells.

Case 11—Female aged 65 Histors—Loss of weight and indigestion for 9 months clinical diagnosis carrinoma of colon Necrops—Skull contained many rounded soft pinksh grey tumours which adhered to both dura and penceranium. All vertebrae contained similar growths several of which perforated cortex and formed hemisphenical

(5) Metabolic aspects of myelomatosis

(a) Bence Jones proteinuria

This is demonstrable in more than one-half of the cases, but is often intermittent and so escapes detection (Wallgren, Geschickter and Copeland, Batts) Moreover, unless this substance is suspected and deliberately searched for, it is apt to be passed over as "albumen" in routine ward tests as probably happened in my Cases III and V Bell has given a good general account of Bence Jones protein and Apitz has discussed in detail the disturbances of protein netabolism in myelomatosis. Abnormal proteins are produced in the tumour cells, appearing as rounded luchsinophil masses (Russell's bodies) or as crystals. Abnormal protein deposits may develop in various mesenchymal tissues and lead to the 'amyloid disease' which occasionally accompanies myelomatosis. The intestine is an important site of massive amyloid deposits (Randall). Amorphous or crystalline deposits sometimes develop in the renal tubules (Lohlein, Bell. Gunn and Mahle). Further investigation is needed in order to determine whether these various deposits actually consist of Bence-Jones protein or some other allied substance or of some other abnormal metabolite

(b) Renal failure

The renal insufficiency which often complicates the later stages of myelomatosis is sometimes due to purely incidental causes, such as arterial disease or pyelo nephritis, but in some cases it appears to be due to obstructive precupitates in the renal tubules (Lohlein, Bell Newis and Edwards, and possibly in my Case III)

(6) Tumours in soft tissues and the question of metastasis

In many cases of myelomatosis the tumours are restricted to the skeleton but in a proportion of latal cases—perhaps one third or one quarter of them—localized tumours or diffuse mfiltrations of the characteristic cells are present in viscera or other soft tissues. The organs most frequently affected are liver, spleen, lymph glands and kidneys, but deposits have been seen also in the lungs heart, skin and subcutts adrenals, thyroid, testes, overries, intestines, stomach, pancreas, uterus, and dura mater (Lohlem, Batts, Churg and Gordon, Newis and Edwards. Armstrong et al., and my Case V)

Are the multiple tumours in bone marrow and the deposits in soft tissues produced by metastasis or by multifocal origin? Probably both processes participate. There is no doubt that the tumours in bones arise multifocally as a system disease of the bone marrow, these growths are often similar in size with no one tumour more than another specifiable as primary, and they are often very numerous or diffuse while the lungs and other viscera show no secondary deposit. While multifocal origin may also be admitted as possible in lymphoid tissues spleen and liver, metastatic colonization more plausibly accounts for myeloma deposits in these organs and especially tor deposits in the kidneys, lungs, and other organs devoid of haemopoietic functions. It is probable then that both widespread origin in susceptible tissues and metastatic dissemination of tumour cells occur in myelomatosis just as they clearly do in the leukaemias (q v). Indeed 'plasma cell leukaemias have been recorded (references by Churg and Gordon), and

rounded radio translucent areas in skiagrams

Radiographic distinction from
multiple metastatic growths is often impossible

Small tumours produce no
elinical tumofaction of the bones and are to be detected only by skiagrams or
necropsy section of the bones. Larger tumours distend or destroy the cortex
project from the bone surfaces, and produce egg shell crackling or pathological
fractures. The fractures may reunite firmly. Spontaneous fluctuation in size or
retrogression of individual tumours is not unusual

(4) Microscopic structure and histogenesis

In 1921 Wallgren in a collected series of 125 cases of myelomatosis found 35 of plasma celled structure. Later studies however, place the percentage much higher than this e.g. Batts found that in 18 of his 23 microscopically examined cases the tumours were plasmocytomas and this applied also to 5 of my 7 cases Identification of the plasma cells is often readily made in smears or sections stained by ordinary methods, but is aided by Unna Pappenheim or other special stains.

In cases in which the tumour cells have not been identified as plasma cells, they have usually been regarded as myeloblastic and sometimes as lymphoblastic or erythroblastic. However, the nature of the cells in these cases is, I think, often very doubtful and there is no justification for attempting to sub divide the disease on the grounds of this or that writer sarbitrary identification of the cells. Certainly in my own Cases VI and VII the identity of the tumour cells remains uncertain they may have been myeloblasts, or lymphoblasts or immature plasma cells—indeed any kind of immature haemopoictic cells. I agree with Geschickter and Copeland and Churg and Gordon that in eases in which the nature of the cells is uncertain, it is best to admit this and to speak of them simply as myeloma cells they are probably only immature forms or variants of the more typical plasma cells of the majority of cases of myelomatosis.

Cappell's findings in his Case 1 of transition forms between plasma cells and myeloblasts and in his Crise 2 of possible transitions between myeloma cells and fibre producing cells are of significance, suggesting that myeloma plasma cells are but variant derivatives of undifferentiated reticulum cells which also have granulocytic and fibroblastic potencies as well. This does not conflict with the customary view, based mainly on studies of chronic inflammatory lesions that plasma cells are related to lymphocytics, for lymphocytes also occur in bone marrow, and arise here from the same stem-cells as the myeloblasts and crythro blasts and all other constituents of the bone marrow. The fact that plasma cell tumours usually arise in bone marrow and do not occur primarily in lymph glands is certainly of interest is regards the histogeness of plasma cells.

The multinuclented cells of plasma-eelled and other myclomas are of no special histogenetic significance except for their multiple nuclei they are similar in structure to the other cells in the tumours. The suggestion that they represent megakaryocytes as in Gunn and Mahle's title 'megakaryoblastic mycloma is unwarranted.

Justified, because the prognosis of solitary plasmoeytoma following adequate surgical or radiational treatment is good. The radiographic appearances of plasmo cytoma are not characteristic and do not enable it to be distinguished from endosteal sareoma giant cell tumour or metastatic growth. The urine of a patient with supposedly solitary plasmocytoma of bone should be examined repeatedly for Bence Jones proteose, its presence must be looked upon as clear evidence of extensive involvement of bone marrow, in spite of negative radiographic findings. If thorough radiographic examination a year or more from the date of tentative diagnosis is unequinocally negative and proteosuria has been regularly absent, it is improbable that signs of generalized myelomatosis will appear later and the tumour may be diagnosed with reasonable certainty as a solitary one That a considerable number of such cases has now been reported suggests that there is a distinct entity solitary plasmocytoma, which is not merely a precocious lesion of the 'system' disease myelomatosis

PRIMARY PLASMOCYTOMA OF SOFT TISSUES

The rare primary plasma cell tumours of soft tissues are almost restricted to the mucous membranes and submucous tissues of the alimentary and respiratory passages of the head and neck the most frequent sites being the nasal eavity and nasopharynx (Claiborn and Ferris, Blacklock and Macartney, Stewart and Taylor, Hellwig) Kaufmann refers also to plasmoeytomas of the buccal cavity tonsil, larvax and conjunctiva. These tumours form single or multiple polypoid or lobulated masses projecting into the neighbouring cavities and sometimes invading the underlying bones. In spite of this latter property, they are usually relatively benign, growing slowly and amenable to local removal or radiation therapy Sometimes however, a plasmoeytoma in this region invades the bones so extensively that it is difficult to decide whether the growth arose primarily in the mucous membranes or the bones as in Stewart and Taylor's second case and in the remarkable case reported by Cappell and Mathers In occasional cases secondary deposits have been present in the cervical lymph glands or else where (McNamara and Rogers) As Claiborn and Ferris pointed out, it is possible that some of the more makenant nasopharyngeal plasmocytomas may really have been secondary deposits from disseminated myclomatosis

Gordon and Walker reported a case of well circumseribed plasmocytoma

of the lung which was treated successfully by lobectomy

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Plasma cell tumors of the nasal and

CLAIBORN, L. N., and FERRIS H W (1931) nasopharyngeal mucosa Arch Sure 23 477

it is quite possible that these and ordinary non leukaemic myelomatosis are but variants of the larger group of neoplastic myeloses which includes also myeloid leukaemia

SOLITARY PLASMOCYTOMA OF BONE

Multiple myclomatosis sometimes first declares its presence by a single prominent tumour in bone and in occasional cases the appearance of this apparently solitary growth precedes that of multiple growths in other bones by a period of many months or even years (Cutler et al.) But there also occur rare cases in which a large destructive tumour of bone proves to be a plasmo cytoma and is not followed by tumours elsewhere in the skeleton but is cured by

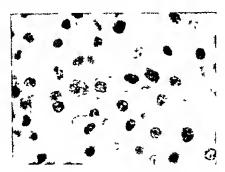


Fig. 382 - Section of solitary plasmocytoma of vertebra (Toluidine blue stain.) (> 1 200.)

amputation or irradiation. For reports and reviews of these solitary plasma-cell tumours of bones are Stewart and Taylor and Willis. In my paper I described a plasmocytoma of long duration in the second cervical vertebra of a man ag.d. 45. (Fig. 382). and reviewed 12 other acceptable cases of solitary growths in bones. The 13 cases comprised 10 men and 3 women of ages ranging from 29 to 68. The bones involved were femur (5 cases usually upper third) verticbrae (3 cases) pelvis (2 cases) humerus (2 cases) and tibla (1 case). Involvement of a long bone was associated with pathological fracture in all but one of the cases.

A correct clinical diagnosis of solitary plasmocytoma of bone can be reached only by (a) microscopical identification of the growth and (b) evaluation of the possibility that the tumour is merely the first sign of generalized myelomatosis (a) involves exploratory operation and (b) complete and repeated radiographical examination of the whole skeleton But, in a suspected case, these measures are

justified, because the prognosis of solitary plasmocytoma following adequate surgical or radiational treatment is good. The radiographic appearances of plasmo cytoma are not characteristic and do not enable it to be distinguished from endosteal sarcoma, giant-cell tumour or metastatic growth. The urine of a patient with supposedly solitary plasmocytoma of bone should be examined repeatedly for Bence-Jones proteose its presence must be looked upon as clear evidence of extensive involvement of bone marrow, in spite of negative radio graphic findings. If thorough radiographic examination a year or more from the date of tentative diagnosis is unequinocally negative and proteosuria has been regularly absent, it is improbable that signs of generalized myelomatosis will appear later and the tumour may be diagnosed with reasonable certainty as a solitary one That a considerable number of such cases has now been reported suggests that there is a distinct entity solitary plasmocytoma which is not merely a precocious lesion of the system 'disease my clomatosis

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CHAPTER 51

OTHER NEOPLASMS OF HAEMOPOIETIC TISSUES

In the preceding two chapters we have discussed tumours of lymphoid tissues and plasma cell tumours. The following neoplastic discusses of haemopoietic tissues remain for brief consideration.

- Myelogenous leukaemia
- 2 Chloroma
- 3 Polycythaemia vera
- 4 Basophil cell tumours
- 5 Monocytic leukaemia "

MYELOGENOUS LEUKAEMIA

Myclogenous leukaemia is but the over-population of the blood stream by malignant leucocytes following neoplastic change in the granulocytic series of cells in the bone marrow. This view, the truth of which is evident alike from the distribution of lesions the cytology of the disease, its lethality, and the analogy with lymphoid tumours and leukaemias is now all but universally accepted Israels (1940) is one of the few modern workers who regard leukaemias as non neoplastic. He bases this opinion on the normal development in vitro of leucocytes from the marrow of leukaemic patients, but it is noteworthy that none of his patients came to necropsy, and that their leucocyte counts were all low, lyng between 14 000 and 32 000 cells per cubic millimetre. Were the cells he depots really leukaemic cells? And even if they were why should neoplastic leukaemic cells not show maturation changes approaching the normal? Many tumours show nearly normal cellular differentiation.

It is unnecessary here to describe the clinical and pathological characters of the disease in detail, these are given in many text books and in Forkner's mono graph. Certain special features only are selected for comment here

(1) Mode of origin

As with lymphoid tumours so with mycloid ones, the extent of the area of tissue suffering neoplastic change is difficult to determine Does this take place in a restricted region of bone marrow or as a widespread system disease of much or all of this tissue? The answer is even more difficult to give than for lymphoid tissues for full examination of the bone marrow is seldom possible until late stages of the disease, when the extent of the primary lesions is obscured by almost universal secondary dissemination and infiltration

Diffuse invasive extension from the primary neoplastic areas and from metas tatic colonies of leukaemic cells must speedily obliterate all evidence of the original extent of those primary areas. That dissemination plays a great part is shown by the widespread diffuse leukaemic infiltrates in many non haemopoietic tissues.

Cosin L (1935) Brit J Surg 23 110

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WILLIS R A (1941) Solitary plasmocytoma of bone J Path Bact 53 77 (Case report and review)

occur in the liver, spleen and bone marrow itself. They are probably responsible for the bulk of the leukaemic deposits in the liver and spleen, in which the occur rence of autochthonous leukaemic change is, I think, very improbable

(2) Age and sex

The more usual form, the chronic form, of myelogenous leukaemia is rare in patients under 30 years of age most cases are in the fourth and fifth decability and the foliation of which are myelogenous, are commonest in young people, according to Warren they occur at three distinct periods, namely, 24 per cent before the 'age of 10, 42 per cent between 25 and 35, and 20 per cent between 45 and 50. Kelsey and Anderson reported a case of congenital myeloid leukaemia and reviewed 9 other recorded cases of congenital leukaemia, of

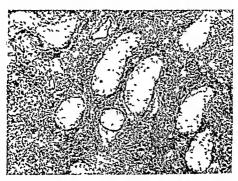


Fig. 385—Testis from a man of 48 years showing severe myelogenous leukaemic infiltration (× 100)

which 8 were myeloid. It is important not to mistake the blood picture of erythro blastosis foetalis for leukaemia. Both chronic and acute myeloid leukaemias affect males about twice as frequently as females.

(3) Cytology

The circulating cells in myelogenous leukaemia are not merely immature cells, but are often structurally atypical defying identification as 'myelogytes', 'metamyelocytes', 'myeloblasts', etc In many crises of leukaemia preuse differential counts are impossible. In the more acute forms of the disease mitotic figures are often seen in the cells in blood films (Bowcock, other references by Forkner, and see Fig. 386). The relative proportions of cells with neutrophil eosinophil and basophil granules vary greatly, cases with great predominance of cosinophil or basophil granulocytes justifying the titles 'cosinophil cell leukaemia' and 'basophil cell leukaemia' are rare (Forkner Lillie) and caution

such as lungs skin kidneys and testes (Figs 383-385). These infiltrates are certainly due to metastatic colonization of the tissues by malignant leucocytes

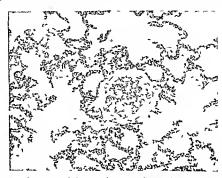


Fig. 383 — Lung from a man of 43 years with severe myelogenous leukaemia whose leucocyte count exceeded 1 000 000 per cubic millimetre showing a blood vessel packed with leukaemic cells and heavy infiltration of the lung septa (x 80)



Fig 384 - Detail of lung septa in Fig 383 (> 150)

brought there by the blood stream and not as was once supposed to autoch thonous extra medullary leucopoiesis. Similar metastatic infiltrates must also

lobulated nuclei as 'megakaryocytes' It is, however, doubtful if these large cells are indeed megakaryocytes, the resemblance amounts to no more than multinucleation or nuclear lobulation and it must not be overlooked that large multinucleated cells may appear in hyperplistic spleen or lymph glands in other pathological conditions not involving "mycloid transformation", as in the peculiar lesion described by Collins Neither the giant cells of Hodgkin's disease nor the multinucleated cells of myclomatosis are megakarvocytes, but large tumour cells of the kind composing the tumour May not multinucleated tumour cells appear also in myclogenous leukaemia? Or may not some of the multinucleated cells in the leukaemic spleen be merely hyperplastic, perhaps phagocytic, reticular cells evoked by the presence of the pathological leucocytes? I do not deny that mycloid metaplasia may possibly occur, but I think the question needs further study with the foregoing possibilities in mind

(7) Myeloid leukaemia in animals

Myeloid leukaemia occurs in dogs cattle, horses mice, rats and probably other mammals, and in birds (Furth et al., Forkner, Feldman, Wilens and Sproul) Lillie reported leukaemia with predominance of basophil myelocytes in a cat

(8) Causation of myelogenous leukaemia

Hueper's book (1942, Chapter VI) contains a good review of leukaemia or leukaemod reactions occurring in persons exposed to benzol, X rays or radio active substances, and in experimental animals treated by benzol, indole, carcino genic hydrocarbons and other substances, or exposed to radiation. Because of the difficulty of distinguishing true leukaemic from leukaemiod blood pictures in some cases, and because the number of reported cases of leukaemia in suspected occupations is still small, the evidence that human leukaemia is caused by extrinsic agents is still inconclusive. But it is at least strongly suggestive, and fully justifies Hueper's recommendation of a 'diligent server in in the occupational history of every leukaemic patient for evidence of a prolonged contact with chemical agents affecting leucopoiesis. Many occupations involve close contact with benzene trimitrotoluene or other volatile organic substances which may damage the leucopoietic tissues, and all drugs or other substances known to be capable of causing agranulocytosis should also be suspect as possible causes of leukaemia.

CHLOROMA

Forkner (1938) gives a good account of chloroma and chloroleukaemia. These rare greenish nodular or diffuse growths may occur in any soft tissues but have a special predilection for periostea. They consist of rounded poorly differentiated actively multiplying cells usually of uniform size and with single spherical nuclei Earlier writers identified the cells as lymphoblastic in some cases and myeloblastic in others, but there is now little doubt that all chloromas are myeloblastic and that they constitute merely one variant of myelogenous leukaemic metastasis, or infiltration. With few exceptions the patients often children or adolescents, have frankly leukaemic blood changes, but these may be overlooked because

is needed not to make a false diagnosis of the former in cases of great eosinophilia from other diseases such as parasite infections. Hodgkin's disease or occasional carcinomas with cosinophilia.

(4) Leukanaemia "

This name is applied to those rare cases in which pernicious anaemia or a pernicious anaemia like blood picture has been followed by the development of myelogenous leukaemia (Forkner Foy et al.)

(5) "Frythroleukaemia

This name refers to cases of associated erythrocythaemia and myelogenous characteria either coexisting or the latter supervening on the former Many cases of this kind have been recorded (Weber, Forkner and see Case II below), the

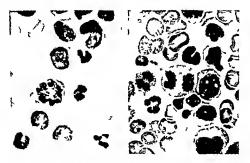


Fig. 386—Mitoses in a blood film from a case of invelogenous leukaemia (× 1 000)

association is too frequent to be purely fortuitous and some actiological relation ship between the two conditions must cust. Perhaps this relationship is that both diseases are neoplastic and that neoplastic change initially affecting the crythropoietic series of cells may later extend to the leucopoietic.

(6) Myeloid transformation ' of the spleen or other tissues

Huge enlargement of the spleen occurs in many cases of chronic myelogenous leukaemia—whence the clinical designation splenomedulary leukaemia Microscopically the enlargement is seen to be due mainly to great accumulation of leukaemia cells often along with some grant cells and it has been debated whether these have arisen from arrested blood borne cells or from myeloid transformation of splenie tissue. Although proof one way or the other may be difficult or impossible the former explanation namely that the splenie disease is essentially metastatic seems to me to be much the more likely. Upholders of the myeloid transformation hypothesis have identified the large cells with multiple or

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In all respects these cells resemble immature nucleated cells of the erythroblastic series Mitotic figures are rare The multinucleated cells vary in size shape and number of

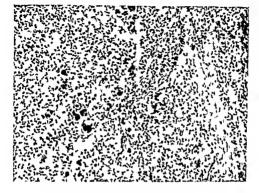


Fig 387 -Case II Malignant erythroblastoma (> 150)

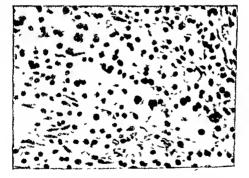


Fig 388 -Detail of Fig 387 (× 500)

nuclei the largest attain diameters of 50 µ or more and contain 10 to 20 nuclei in a section usually situated in a concentric zone about midway between the centre and periphery of the cell The cytoplasm of the large cells is homogeneous and eosinophilic

attention is often focused on a clinically obtrusive tumour of the skull, spine or some other part. In most cases the disease runs an acute course and proves fatal within a few weeks or months chronic cases are rare. The green colour of the tumours fades on exposure to oxygen but may be restored by hydrogen perovide Feldman gives references to chloroma in pigs and eatile and Wilens and Sproul saw conspicuous examples in leukaemic rats

The following case exemplifies chloromatous infiltrations accompanying other wise ordinary myelogenous leukaemia

Case I—Male aged 25 was under treatment for some months for typical myelogenous leukaema the leucocyte count reaching 300 000 per cubic millimetre and showing a high proportion of immature cells. Accrops—Liver 71 pounds pale and mottled contains one greenish tumour 15 centimetres in diameter. Spleen 174 pounds pink with dusky greenish patches. Lymph glands moderately enlarged soft green. Left spermatic cord thickened by greenish infiltration. Skeleton bone marrow of vertebrae and femor greenish skull normal other bones not sectioned. Other organs show pallor only On exposure to air for half hour green colour of tissues had faded. Histology—Typical myeloid leukaemie infiltrations with focal timout like aggregations in places.

From my department Laurie described an unusual case of chloroma with well defined metastatic plaques on the dura mater. In another case on which I performed the necropsy there were extensive paravertebral lesions with para plegia and the patient had been operated on for 'spinal tumour'

POLYCYTHAEMIA VERA OR ERYTHRAEMIA

For clinical and pathological details of this disease consult Weber's excellent monograph (1921). All that is intended here is to express agreement with Weber serve (1936) that this disease is probably a primary neoplastic process in the erythroblastic portion of the bone marrow analogous to myelosis (myeloid leukaemia) in the leucoblastic portion. This view is supported by the more than fortuitous association of crythraemia and leukaemia already referred to and by cases like the following in which a malignant hiemopoietic (almost certainly crythropoietic) neoplasm without leukaemia supervened on polycythaemia.

Case II - History - In 1929 a man aged 31 attended hospital because of haemoptysis and was found to have splenomegaly red-cell count 8 850 000 and Hb 130 per cent Treated by X rays and phenylhydrazine he remained fairly well but continued to have attacks of haemoptysis In 1940 red-cell count was 8 500 000 and Hb 140 per cent Late in 1942 he began to lose weight and strength, and his colour rapidly changed from purple to pale in January 1943 red-cell count was 4 million. Hb 55 per cent white cell count 12 500 (62 per cent neutrophils 30 5 per cent lymphocytes) Patient died in February at age of 45 years Necropsy-Liver enlarged pale and mottled spleen 41 pounds pale red mortled with white areas kidneys contain ill-defined white areas lymph glands all appear normal. Vertebrae and ribs contain many irregular areas of white growth replacing marrow and forming smoothly rounded supperiosteal swellings up to I centimetre deep skull normal but dura mater of left middle fossa contains a projecting plaque of soft white growth 3 centimetres in diameter Histology (Figs 387-389) - Dural skeletal and renal growths consist of mingled mononucleated round and multinucleated giant cells with all intermediate forms. The mononucleated cells pre dominate they are well defined average about 10 un diameter contain dense darkly stained spherical nuclei about 6, in average diameter and their homogeneous cytoplasm is distinctly cosmophilic in most cells but faintly basophilic or polychromasic in others

diameter about 15u with single rounded or reniform nuclei and extoolism decistudded with fine strongly basophil granules similar to those of next case

Case IV -For some months a slowly enlarging soft pendulous tumour of the same had been noticed in a male English setter aged 12. The dog was destored able tumour removed but the viscera were not examined. The lumour measured 5 courses in diameter was unconnected with the testes and arose from the scrotil will be consisted of pliable tissue resembling mingled soft fibrous and adipose tiss... 2.1 was clothed by thin skin Histology-Similar to previous case but tissues more her



Basophil-cell tumour from a dog (Inset slightly retouched) (t)[Fig 390 -- Cust 11 and 500 i

infiltrated by the basophil granular cells which were fully studied by Lectural Clemba statute also the agent Giemsa stains also (Fig. 390)

MONOCYTIC LEUKAEMIA

monocytic leukaemia have been described and reveal h Dameschek Clough Campbell et al., and Forkner Some workers, e.g. Farter think this disease. think this disease is an entity distinct from other kinds of leukaemia, city with whom I also among the state of the state with whom I ally myself contest this and believe that "monocyte" ledies is usually myclored lend contest this and believe that "monocyte" ledies is usually myclored lend contest this and believe that "monocyte" lend or with reconstructions. is usually mycloid leukaemia with monocytoid mycloblasts of with 1861 monocytosis (Naegeli) of the with monocytoid mycloblasts of with 1861 monocytoid myclobiasts of with 1861 monocytoid myclobid myclo monocytosis (Naegeli), or that it is only a variant of lymphatic leukaemia (it is only a variant of lymphatic leukaemia (it is only a variant of lymphatic leukaemia (it is only a variant of lymphatic specific distinct specific specific distinct specific specific distinct specific d To me as to Guiland and Cooling a variant of lymphatic tecksome (the coll but only a variant of the coll but only a variant onl cell but only a variant of the codall the monocyte is not a distinct special films all transitions can be to whole lymphocyte mononuclear senes, and promonocytes.

This communication is a proper to the control of the monocytes This opinion haraced between "typical" lymphocyte and fyd fed by strengthened by my examination of the reported cases of the strengthened by my examination of the reported cases of the strengthened by my examination of the reported cases of the strengthened by my examination of the reported cases of the strengthened by my examination of the strengthened by the str films from several cases of stars been strengthened by my examination for reported cases, most of stars been strengthened by my examination of feed reported cases, most of stars been strengthened by my examination of feed reported cases, most of stars and by most of stars and stars and by most of stars and star reported cases, most of the prosed "monocytic leukaemia and by grading from the property of th Transition forms between the small and large cells are plentful. Spicen shows patches and diffuse infiltrations of similar cells so also do some lymph glands. Liver shows many small intravascular foct of mononucleated cells resembling crythroposetic foct and the situation masses of chromatin (Fig. 389). Comment—The morphology of the timour cells shows almost conclusively that they are abnormal pleomorphic cells of the crythroposetic blastic series. I interpret the case as one of true polycythaemia terminating in malignant crythroblastoms with disseminated metastatic lessons in liver spleen lymph glands kidneys dura mater and possibly in the home also the condition is the crythroblastic analogue of mycloid leukaemia with metastatic tumours and infiltrations. There was no sign of maturation of the tumour cells to form crythrocytes. Perhaps pare passu with the enhanced malignancy of crythroposetic growth the capacity to maturate was lost this change corresponding with the sudden clinical change from simple (benign)

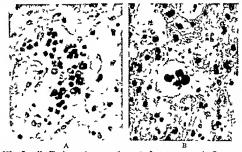


Fig. 389—Case II The liver A= an erythropoietic focus in a sinusoid B= a syncytral mass in a sinusoid (y 500)

polycythaemia to the non-polycythaemic state. As Parkes Weber suggests polycythaemia may be regarded as a relatively benign neoplasm: the foregoing case illustrates its more malignant counterpart.

BASOPHIL CELL TUMOURS

Excessive numbers of basophil granulocytes may be seen in myelogenous leukaemia but I know of no records of localized basophil cell tumours in man Rudduck and I studied the following two instances of such tumours in dogs

Case III—For 4 years a male pug dog aged 14 had had slowly enlarging soft pendulous tumours of the skin of the neek, chest and perineum theanimal was destroyed. Accepts 10 No visceral lesions were found. The 3 largest skin tumours measured 10 5 and 4 centimetres in their main diameters, there were several smaller tumours also. These all consisted of lax finely spongy fibrous-looking tissue not encarpsulated but clothed by thin intact skin. Hutol-px—Dermal and subcutaneous tissues show marked general increase of connective tissues and many new formed blood viscels. These tissues are lightly or heavily infiltrated throughout by darkly stained rounded cells of average.

CHAPTER 52

THE GLIOVIATA

In the strict sense ghoma means a tumour of neuroglal tasks to the non mesenchymal stromal tissue of the central nervous system. The includes the astrocytes objected and evendyma, ghoras a grad derived from and composed of cells of these types The term is how a month extended to embrace three other kinds of growth not dented to ordinary neuroglial tissues-medulloblastoma and neuro-ep delena r tumours of embryonic nervous tissue, and pinealoma · Ghoma standar be used to include ganghoneuromas of the central nervous system (E mail these ever occur see Chapter 55) tumours of the choroid plexuses (Ch. or tumours of the mesenchymal tissues of the nervous system or its them The view espoused by many French workers that these last named ussues a neuro-ectodermal origin and the corresponding practice of designating to and nerve-sheath tumours peripheral gliomas cause needles confusion

As I am sceptical of the value of complicated sub-divisions of the and hold seemingly over-simplified views regarding their histogenesis and kind it is necessary to state briefly the extent of the material from which tho were derived. At the Alfred Hospital Melbourne from 1930 to 1945 1 1 good fortune to be closely associated with Mr H C Trumble's active E surgical clinic and to carry out in collaboration with Dr L B Cot a carry microscopical study of nearly 300 surgical biops, specimens of ghomas and e 136 necropsies of cases of primary intracranial tumours including 84 glionals In the microscopical study of nearly 100 specimens in the early part of the series we employed not only the more usual stains but also the metallic impregrand methods of Cajal Hortega and Bielschowsky with which Cor made man beautiful preparations described in an important paper by him in 1933 The after however these special methods were used less and less for we becar increasingly convinced that they are much less specific than is often assumed that in tumours of doubtful nature their results are often difficult to interpreand that in only occasional cases did they yield definite and helpful information not obtainable by the more usual staining methods

of lymphatic leukaemia and to be monocytic only in that the appearances of some or many of the abnormal cells resemble those arbitrarily accepted as typical' of monocytes

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poorly differentiated cells ("glioblastomas") often show areas of recognizable tumour astrocytes. Indeed the frequent presence of such areas makes it clear that most 'glioblastomas are anaplastic astrocytomas. It is highly probable that they all are, but it is not possible to affirm this, since some of them are completely anaplastic and lack all signs of differentiation. A further objection to the -blastoma terminations has already been mentioned namely, their embryological implication. A stroblastomas' and 'spongioblastomas' are not, as the names imply, tumours of immature embryonic cells but anaplastic tumours derived from adult tissues. It is particularly important to avoid this false implication of an embryonic origin, since there is a glioma the medullo blastoma, which is truly embryonic

(d) The growth patterns of gliomas are unsafe grounds for creating sub divisions

The patterns of ghomas are partly determined by their intrinsic habits of growth and partly by the pattern of the invaded tissues Scherer (1938) has empha sized this point and has shown that gliomas of intrinsically homogenous arrangement assume different patterns in grey and white matter, and that prominent perivascular or fascicular arrangement is often determined more by the pattern of the pre existing structures than by the habit of growth of the tumour cells themselves. It is therefore unsafe to use growth patterns or the shapes of the cells as bases of classification. In one area an astrocytoma may consist of plump asteroid cells devoid of polarity in another area of bundles of compressed fusiform cells and in another of elongated cells arranged radially around blood vessels Tumour astrocytes or their anaplastic derivatives vary greatly in size and shape, they may be stellate fusiform, pyriform or multiform, they may be arranged loosely, compactly, in broad or narrow strands or in perivascular mantles they are all still astrocytes. Cox fully described the great variations in shape of tumour astrocytes according to their positions and state of health. It is clear that Bailey and Cushing's 'spongioblastoma unipolare' (Penfield's 'polar spongioblastoma') is, as Cox suggested and as Russell and Bland proved by tissue culture, a fusiform celled or 'piloid' astrocytoma And I have already expressed my conviction that the so called 'ependymal spongioblastoma' is often only an astrocytic glioma with prominent perivascular radial arrangement of elongated cells Adjectives the "multiorme", 'unipolare' 'pilod' "giganto cellulare', fibrillar and 'fascicular', used in naming gliomas have only a descriptive value and are of no significance as regards histogenesis and classification

(e) Included cells af invaded tissues have often been misidentified as tumour cells

Cox made a special study of this subject and pointed out how the inclusion of nerve cells and fibres within gliomas or of non neoplastic astrocytes within medulloblastomas might lead to errors of interpretation and classification

(f) The metallic impregnations are only relatively specific

This deserves repeated emphasis. It is true that typical normal astrocytes oligodendrocytes nerve cells and fibres or their well differentiated neoplastic counterparts, may show distinctive staming properties when appropriately fixed and treated. But it is also true, (i) that the metallic impregnations are often

the reduction of the number of sub-groups and names to the barest possible minimum

(a) The three types of normal neuroghal cells are not sharply distinct

Histologists recognize that while typical astrocytes and oligodendrocytes differ in form and staining properties, there are many transitional forms (Maximow and Bloom, 1944) Ependymal cells and immediately sub ependymal astrocytes are similar in cytoplasmic and nuclear structure and probably differ in form only because of their positions Too much stress has been placed on the presence of blepharoplasten in ependymal cells, this relatively minor feature does not imply sharp distinction from sub ependymal cells.

(b) The corresponding three types of gliomas are not sharply distinct

While it is true that many gliomas consist mainly or wholly of eells with the typical forms and staining properties of astrocytes and a few gliomas consist of cells with the typical forms and staining properties of oligodendrocytes, many tumours contain both types of cells with transitions between them Bailey and Buey Kwan and Alpers, and Cooper described transition forms between oligocytes and astrocytes in oligodendrogliomas, and Cooper particularly stressed the frequency of mixed 'oligo astrocytomas My own experience accords with Cooper's I have seen more tumours of mixed or transitional structure than pure oligodendrogliomas. So also many of the tumours designated ependymomas are not sharply distinct from astrocytomas Relatively few of these tumours have contained eavities lined by unmistakable ependyma most of them have shown only a radiating arrangement of bipolar eells around blood vessels (Bailey and Cushing Bailey 1932 Bailey, Buehanan and Bucy 1939) and these bipolar cells or so-called ependymal spongio are often brilliantly impregnated by the gold sublimate method and show transitional forms between the simple polar shapes and undoubted ocytes (Cox) My own findings accord with this and I agree with Cox's ision that the 'ependymal spongioblast is nearer in structure to astrocytic series than to adult ependyma? Indeed, I doubt the validity of the ms ependymoblastoma 'ependymal spongioblastoma' or ependymoma" oplied to tumours of this kind these names have often been uncritically applied to astrocytomas with prominent persoascular mantles of elongated cells. The only tumours unquestionably deserving the name ependymoma, are those with ependyma lined cavities and these are rare

ng degrees of and -not mean distinct types of tumours Il differentiated -- lled an astrocytoma well different ld not be called toma nor ? spongio or gliobias rocytic they differ of ation ele tumou Lagree 40) th it most entrated posed of

(c) Ependymoma

In my opinion, the name should be applied only to tumours containing spaces lined by ependyma Such tumours are rare

(d) Medulloblastoma and neuro epithehoma

These are truly embryonic tumours arising from developmentally still immature nervous tissue, the former composed of diffuse masses of small embryonic cells, the latter (extremely rare) showing spaces lined by layers of embryonic neuro conthelium

It is necessary to mention, in order to dismiss, two recently advanced hypotheses regarding the histogenesis of gliomas. One of these, put forward by Singer and Sciler (1933), is that the parenchymn of the gliomas is not neuroglial but neurome and that their glial content is merely stromal. The other view, advanced by Globus and Kuhlenbeck (1942) revives Cohnheim's embryonic cell rests and supposes gliomas to 'take origin from unripe neuroectodermal derivatives" and to undergo differentiation into "both neural and ghal elements". Except in so far as medulloblastomas are embryonic tumours with therefore some latitude of potencies for differentiation neither of these hypotheses need be considered seriously—the simple neuroglial nature of the adult gliomas is beyond question. The writers eited and many others have mistaken altered astrocytes or included nerve cells for neoplastic nerve cells.

I commend to the reader Russell's 1939 paper as an excellent outline of the pathology of the gliomas and other intraeranial tumours

SEX. AGE AND SITE INCIDENCE OF GLIOMAS

(1) Sex

The seves are nearly equally liable to gliomas Males have predominated in some series, e.g. my necropsies were on 51 males and 33 females and Courville's collection of multiple gliomas comprised 77 males and 38 females Medullo blastomas of the eerebellum appear to predominate in males (Bailey et al)

(2) Age

The age distribution curve for all gliomas (Bailey et al) shows two peaks, one in the second hemi decade the other in the fifth decade, with a trough in the later part of the second decade. The first peak is due to the frequency in young children of medulloblastomas and cerebellar astrocytomas, tumours which are relatively rare in later life. The peak in the fifth decade is due to the gradually increasing incidence of cerebral astrocytomas and "glioblastomas", which are common in adults but rare in children.

(3) Gliomas in children

Of 75 gliomas in children recorded by Bailey et al, 30 were classified as astro cytomas (the majority cerebellar) an additional 26 were in my opinion probably of astrocytic origin (7 "ependymomas", 10 'spongioblastomas', 7 "glioblastomas' and 2 astroblastomas"), and 13 were medulloblastomas nearly all cerebellar The mean age of Bailey and Cushing's 25 cases of cerebellar medullo blastoma was 10 years. All 15 of their cerebellar astrocytomas were in young

fickle failing to impregnate the appropriate cells for no known reason or sporadic ally impregnating cells other than the appropriate ones (ii) that pathological tissues have seldom been subjected to standard treatment as regards the time elapsing between their removal and fixation the nature and purity of the fixatives used the time of fixation, and other unknown factors these being particularly relevant as regards necropsy and museum material and (iii) that tumour cells are tumour cells, manifesting varying degrees of anaplasia with abnormalities both of form and of staining properties. For these reasons, when interpretation of the nature of a particular tumour is difficult from tissues stained by the ordinary methods interpretation of the metallic impregnation results is almost always more difficult still and it becomes merely a matter of arbitrary opinion as to which method to rely on most. The following statement by Bailey et al. (1939) in reference to several figures of neuroblastoma in his and Cushing's earlier 'On the basis of these silver impregnations, we monograph is significant classified two tumors as neuroblastomas, which we have since come to doubt The reduced silver method of Caial is not specific even on normal tissue unless modified for each type of neurone which one wishes to demonstrate and used on tissue specially fixed for the method The Bielschowsky method is very unspecific under any circumstances. To which I would add that the multiplicity of the modifications of the metallic impregnation methods which have been and are used is clear evidence of their non specificity, and also a further source of endless confusion The most reliable of the metallic impregnations is Cajal's gold ehloride sublimate method for astrocytes, but when it gives positive results, the astrocytic nature of the cells is seldom in doubt from preparations stained by the ordinary methods

The elassification adopted

It will be clear that I do not favour rigid sub division of the gliomas. But for descriptive purposes three main structural types corresponding to the three types of normal neurogiral tissue may be recognized to which must be added the truly embryonic tumours. We thus have the following sub groups

(a) Astrocytic glioma

This group includes astrocytoma composed of well differentiated stellate cells astroblastoma composed of imperfectly differentiated stellate cells astrocytoma giganto cellulare composed of large pleomorphic cells (often closely resembling nerve cells) spongioblastoma or glioblastoma multiforme composed mainly of pleomorphic poorly differentiated anaplastic cells most 'e-pendymail's pongioblastomas' (the cpendymain' of most writers) composed of clongated cells arranged and fascicular forms of piloid astrocytoma composed of clongated cells arranged in bundles. All of these are merely structural variants of a single species and several of them may be found in one tumour.

(b) Oligodendroglioma

This name is appropriate for tumours composed wholly or predominantly of cells recembling oligodendrocytes. They are not sharply distinct from astrocytic gliomas. transitional or mixed tumours are common.

(c) Ependy moma

In my opinion the name should be applied only to tumours containing spaces lined by ependyma Such tumours are rare

(d) Medulloblastoma and neuro-epithelioma

These are truly embryonic tumours arising from developmentally still immature nervous tissue, the former composed of diffuse masses of small embryonic cells, the latter (extremely rare) showing spaces lined by layers of embryonic neuro epithelium

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people of meanage 13 The meanage of Bucyand Gustafson s 25 cases of cerebellar astrocytoma was 9 years, with a range from 21 months to 22 years My 84 necropsy cases of glooma included 13 under the age of 20 the tumours were 7 medulloblastomas 4 astrocytomas (3 in the cerebellum) and 2 diffuse cellular tumours of undetermined nature Russell and Ellis reported a large "polar spongioblastoma" in the cerebrum of a still born full term foctus

(4) Gliomas in adults

With infrequent exceptions these are astrocytic tumours of the cerebrum, cerebellar ghomas in adults are relatively infrequent. Poorly differentiated growths— multiform ghoblastomas'—rather outnumber well differentiated astrocytomas, but all transitions and combinations occur. The well differentiated astrocytomas occur on an average decidedly earlier than the more anaplastic growths the former being most frequent in the third decade and the litter in the fourth and fifth decades. Oligodendrogliomas are almost restricted to adults. Bailey et al. found only one example amongst 75 glioms is in children

(5) Sitcs

The cerebellum and fourth ventriele are thus the commonest sites of gliomas in children the cerebrum is the commonest site in adults The brain stem is an infrequent site but appears to be relatively more often affected in children than in adults when glioblastomas' occur in children they are usually situated in the pons (Bailey et al.) Gliomas of the spinal cord are uncommon but may be of any of the types seen in the brain. Kernohan et al. depicted examples ependymoma' spongioblastoma "astroblastoma" oligodendroglioma and medulioblastoma but gave no details of the eases. They noted the frequent association of spinal gliomas with syringomyelia Cox (1937) also saw an intramedullary glioma associated with syringomyelia Gliomas of the optic nerves or chiasma are rare tumours, least uncommon in children and young people (Verhoeff Martin and Cushing Bailey et al.) I know of no acceptable report of glioma of the par nervosa of the pituitary gland. True astrocytic gliomas of the retina are described in Chapter 57

(6) Multiple gliomas

These are not unusual Coursille reviewed 134 cases including 21 of his own and he estimated that multiple growths occur in about 8 per cent of cases of glioma. Most of the patients were adults most of the tumours were in the ecrebrum and multiplicity was more frequent with multiform glioblastomas than with astroeytomas—10 per cent and 6 per cent of cases respectively. In most cases 2 tumours were present but cases with 4 or 5 separate growths were observed. These were sometimes situated in one hemisphere sometimes in both hemispheres sometimes in one hemisphere and the corpus callosum. Needless to say careful dissection and microscopical study are necessary before concluding that two neighbouring growths are indeed distinct. My own series of 84 necropsies included 2 with certainly multiple gliomas—2 tumours in cach case. With rare exceptions multiplicity cannot be explained by metastasis and is clearly due to multifocal origin.

(7) Diffuse gliomatosis

This is an appropriate name for those not unusual astrocytomas which diffusely affect extensive areas of the brain, their limits cannot be determined by the naked eye or even with the microscope. Nevin recorded good examples with excellent illustrations. The well differentiated tumour astrocytes, barely or not at all distinguishable from normal ones, are mingled intimately with the normal tussues, which show general swelling, pallor and blurred pattern but without losing their main structural markings or suffering any great change of consistency. Such tumours may affect a large part of one or both hemispheres



Fig. 391—Well differentiated astrocytoma of cerebrum of a woman of 47 years with 11 years history of fits—successful removal of lobulated tumour 5 centimetres in diameter. (× 150)

Their diffuseness cannot be attributed wholly to proliferative invasion of the surrounding tissues, I agree with Scherer (1940) that they are primary diffuse neoplastic proliferations of the neurogla of considerable areas of the brain?

(8) Heterotopic gliomas

Heterotopic neuroglial tissue in the meninges has been observed by several workers (references by Bailey, 1936) Bailey described a meningeal astrocytoma presumably derived from such heterotopic tissue. Needless to say, in any case of this kind before the diagnosis of primary meningeal glioma or gliomatosis can be accepted as certain it must be shown that the brain and spinal cord contain no primary glioma to which the meningeal disease is secondary. Bratton and Robinson described two extra-cranial gliomatous tumours in infants, one of the palate and one of the subcutaneous tissues of the nose, the palatal tumour may have been a teratom with predominant development of neural tissues but

people, of mean age 13 The mean age of Bucy and Gustafson s 25 cases of cerebellar astrocytoma was 9 years with a range from 21 months to 22 years My 84 necropsy cases of glioma included 13 under the age of 20, the tumours were 7 medulloblastomas 4 astrocytomas (3 in the cerebellum) and 2 diffuse cellular tumours of undetermined nature Russell and Ellis reported a large 'polar spongioblastoma' in the cerebrum of a still born full term foetus

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descriptive adjectives like solid and cystic, circumscribed and diffuse, stellate celled and polar celled, while usefully applicable to particular tumours or to par

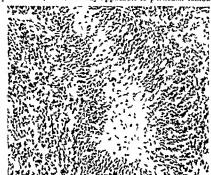


Fig. 393—A well differentiated fibrous astrocytic area in a cellular—glioblastoma—of cerebrum—of a man aged 35—(× 150)

ticular parts of one tumour do not denote distinct types of growths The "piloid" tumours are only a variety of conspicuously fibrillar astrocytoma with elongated

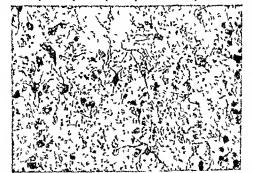


Fig. 394.—Tumour astrocytes in an astrocytomatous area of a cellular glioma of cerebrum (Cajal's gold-chloride sublimate method) (×250)

cells Cox, Alpers and Rowe, Scherer and Bucy and Gustafson are amongst those who have stressed the diversity of cytology in the astrocytomas

the nasal tumour consisted of astrocytic neuroglia only and was evidently derived from developmentally separated tissue

THE MAIN STRUCTURAL TYPES OF GLIOMA

I do not intend to repeat in detail the structural features of the commoner kinds of glioma. These have already been partly dealt with in the preceding discussion, they are illustrated in Figs. 391 to 403, and full details and many other illustrations will be found in the various papers cited. Here will be given only a brief synopsis of each type, with stress on some special points.

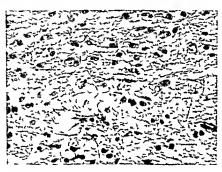


Fig. 392 - Highly differentiated fibrous astrocytoma of pons of man of 43 years (× 400)

(1) Astrocytic gliomas

Tumours of astrocytic origin constitute about three quarters of all gliomas Tumours show great diversity of structure and behaviour. This diversity justifies attempts to sub divide the group for practical prognostic purposes but it must be clearly recognized that the distinctions made are merely descriptive and utilitarian and not histogenetic. The most benight unmours of the group are the slowly growing errcumseribed often cystic cerebellar instrocytomas of childhood the most malignant are the anaplastic pleomorphic-celled glioblastomas but all possible combinations and transitional forms of growth are encountered (See Figs. 391–399)

Astrocytomas are composed mainly of well differentiated astrocytes stellate or elongiated and of more or less abundant ghal fibres. The distinction formerly made between protoplasmic and fibrillary astrocytomas is artificial and indeed pointless since all well differentiated astrocytic tumours contain ghal fibres. Bailey et al. (p. 434) admitted that it would be better to saw more fibrillary or less fibrillary or less fibrillary.

oligodendroglia to typical astrocytes can be found 'Cooper re emphasized this

Calcification occurs in many obgodendrogliomas as in other brain tumours it usually commences around the blood vessels which often become mapped out prominently by their calcific sheaths

(3) Ependymomas

It will already be clear that in my opinion many of the tumours designated ependymoma or 'ependymoblastoma' do not deserve that name but are merely one variety of elongate celled astrocytoma. The term ependymoma

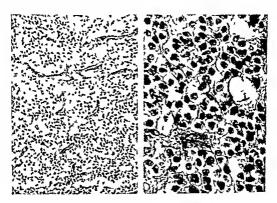


Fig 400 -Oligodendroglioma of cerebrum of man aged 46 (> 120 and 400)

should be applied only to tumours in which spaces lined by unmistakable ependy mal cells are present. As Russell (1939) has pointed out, not a few of the tumours reported as neuro epitheliomas "with rosettes are really ependymomas with cavities lined by well differentiated, often ciliated ependymal cells. The ciliated cells arranged in rosettes show neuroglial processes and fibrils at their outer ends. True ependymomas are relatively benign slowly growing tumours their most usual sites are near the ventricles or in the spinal cord or filiam terminale. One of Cox's specimens which I also examined, was of particular interest in that it consisted partly of ependyma lined lobules with cores of astrocytic tissue and partly of tissue with the structure of 'ependymoblastoma' composed of perivascular mantles of radiating elongated cells which, however had the typical staining properties of astrocytes. This tumour showed the close kinship of epen dymal tumours and astrocytoms.

Two clinico pathological sub groups of the well differentiated astrocytomas may conveniently be recognized without, however, supposing a clear cut distinction

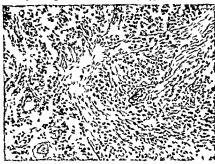


Fig. 395 —Well differentiated fibrillary area in a cellular astrocytoma of cerebrum of a woman aged 23 (x 120) or any fundamental histogenetic difference. These are (i) well circumseribed

or any fundamental histogenetic difference These are (i) well circumscribed benign astrocytomas usually in children usually cerebellar and us<u>ually cystic</u> and (ii) poorly eircumscribed infiltrating astrocytomas usually in adults usually

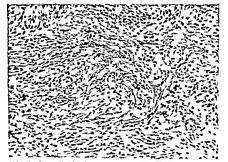


Fig. 396 —Fusiform-celled fibrillary area in the same tumour as Fig. 395 $\,$ (\times 120)

cerebral and usually non-cystic. The benign cerebellar astrocytomas are well described by Bergstrand. Bucy and Gustafson, and Bailey et al.

not helpful in studying these small indifferent cells, which have been identified by some workers as neuroblasts and by others as spongioblasts. The elongated cells



Fig. 401 —Rosettes in a diffusely cellular medulloblastoma of cerebellum of a boy aged 11 (\times 200)



Fig. 402 — Diffuse spread of medulloblastoma in meninges B = surface of brain P = com pact layer of tumour cells on pial surface M = less compact tumour in sub arachnoid space $(\times 120)$.

in some tumours have fine fibrillar processes, with staining properties like thoses of astrocytes, and there is little doubt that in the more slowly growing tumours

kernohan et al stated that they had seen 6 tumours of the spinal cord containing canals lined by ependymal epithelium and their Fig 2 depicts two of these. But they gave no details of their cases, and their description of one of the growths as closely resembling choroid plexus with papillary epithelial structures containing cores of connective tissue does not suggest ependyma. Is it not possible that this tumour and perhaps others may have been metastases from unsuspected primary epithelial growths elsewhere?

I am not convinced of the identity of the tumours in some other reported cases of "ependymoma", e.g. Cases I and 2 of Bailey et al. In such cases unless the whole tumour has been thoroughly studied the possibility of it having been a teratoma with plentful neuro epithelial and ependymal components cannot be excluded. The younger the patient the greater is this possibility. An embryonic ependymoma if such ever occurs would be identical with neuro epithelioma (see below).

(4) Medulloblastomas

Medulloblistomas are far from rare, indeed in children they are only slightly less frequent than the cerebellar astrocytomas. Bailey (1932) recorded 55 medullo blastomas in a series of 378 gliomas from people of all ages. Earlier reports of these tumours referred to them as sarcomas of the cerebellum or meninges (references by Willis, 1934) but the descriptions enable us to identify many of these with confidence as medulloblastomas. Amongst the best recent accounts are those of Cairns and Russell Wanke, and Bailey et al.

(a) Age site and sex incidence

Most of these tumours occur in infants or young children and their usual situation is in the vermis of the cerebellum or roof of the fourth ventricle. They are much less frequent in young adults and in the cerebrum. Bailey and Cushing recorded 25 cerebellar eases of mean age 10 years and 4 cerebral eases of mean age 36. Most medulloblastomas in adults are in young people. I have seen 3 cases of ages 25. 30 and 32. Bailey, Buchanan and Buey reported 13 cases of cerebellar medulloblastoma in children of average age 64 years. 9 of the cases were between 3 and 6 years old. 10 of the 13 children were boys corresponding with Cushing 8 experience that these tumours were three times more frequent.

Relevant to the ages at which medulloblastomas are discovered is the rate at which they grow. They are usually regarded as rapidly growing tumours with a symptomatic duration of only a few months. But as Cox noted eases of long duration are encountered in one of our necropsy eases with a large fairly well defined but microscopically characteristic tumour of the roof of the fourth ventricle in a boy of 11 years, there had been signs of internal hydrocephalus for more than 5 years.

(b) Structure and growth

The tumours are highly cellular composed of small cells of rather uniform size and shape rounded or pyriform or elongated arranged usually diffusely but occa sionally in rosettes clumps or drifts (Figs 401-403) Special stains are usually

• granular layer of the foetal eerebellar cortex. It is of course easy to deduce too much from mere resemblance, but the suggestion that the cerebellar medullo blastomas represent immature cerebellar cortical tissue is supported also by their usual situation and their age incidence. If this view is correct, the cells are immature cerebellar neuroblasts and spongioblasts. Their failure to display conspicuous nerve cell differentiation would not be surprising, for the small cells of even fully differentiated cerebellar cortex do not possess highly distinctive characters permitting their ready identification. In an embryonic tumour it might well be impossible to distinguish immature neuroblasts of this kind from immature spongioblasts.

(5) Neuro-epithelioma or medullo epithelioma

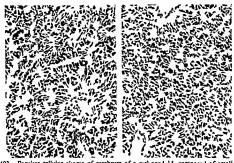
'Medullo epithelioma was the name introduced by Bailey and Cushing to denote tumours containing spaces fined by layers of primitive neuro epithelium resembling that of the embryonic medullary plate "Neuro epithelioma" has been applied to tumours of prominently rosetted structure. While it is quite probable that truly embryonic neuro epithelial tumours exist there is no doubt that these names have been improperly applied to several different kinds of growths, some of which are not embryonic. The fallacies and difficulties of this subject are as follow.

- (a) Adult ependymomas have been mis identified as 'neuro epitheliomas". As Russell (1939) pointed out, this applies to Bailey and Cushing s original report as well as to many later reports. Adult ependyma has cilia and adult ependymomas may contain eavities surrounded by rosettes of eiliated cells. The 'neuro epithelioma' in a man of 65 reported by McLean and Lantiere is a good example of misapplication of the name to a well differentiated ependymoma. Probably most supposed 'neuro epitheliomas in adults are ependymomas.
- (b) Even choroid plexus tumours have been mistaken for embryonic tumours. Thus Greenfield described as a primary "medulio epithelioma" of the cauda equina in a man of 48 years a tumour which was accompanied by a papillary growth in the fourth ventracle and by deposits of similar growth in the eisterna magna and thea, and the figure shows plainly a papillary tumour of the choroid plexus.
- (c) A teratoma with abundant neural tissue could easily be mistaken for a neuro epithelioma." Distinction between the two could only be made with certainty by thorough microscopical study of all parts of the growth and this has seldom or never been carried out on reported cases. Conse quently while it is possible that the tumours containing undoubted embryonic neuro epithelial tissue described by Bucy and Munice, Greenfield (first case) Bailey et al (1939 Fig 85) and by Hirsch and Oldberg were indeed pure embryonic neuro epithelial growths, this remains uncertain Of the 4 tumours just cited, 3 were from the neighbourhood of the fourth

transitions to astrocytic cells can sometimes be traced. This applied to one of Cox's tumours and to two others which I have examined. In making this interpretation, it is of course important not to be misled by residual included astrocytes of the invaded tissues. The evidence for the differentiation of nerve cells within the tumours remains inconclusive. The growths display a remarkable proclivity for diffuse invasion of the leptomeninges and also of the nervous tissues (see below)

(c) Histogenesis

The precise origin of medulloblastomas is still uncertain, but from their cytology and age incidence there is little room for doubt that they are truly embryonic tumours arising from still immature neural tissues during foetal life



Fio 403—Peculiar cellular glioma of cerebrum of a girl aged 14 composed of small angular undifferentiated cells arranged uniformly in small clumps and roseties provisionally classified as medulloblastoma (x 150)

or early childhood. In this respect they are comparable with the neuroblastomas of the sympathetic system and the retinoblastomas, though of course it is a mistake to confuse these three distinct kinds of embryonic neural tumours as some writers have done.

Bailey and Cushing introduced the name medulloblastoma to suggest that the growths consisted of immature bipotential cells akin to Schaper's indifferentiated cells of the developing brain. Embryologists have observed that proliferating undifferentiated cells persist in various parts of the growing brain long after birth and that this post initial prohleration is much more active in certain regions especially that of the rhombic lip from which formation of the cerebellar cortex proceeds and which is the favourite region of origin of medulloblastomas. Tuthill found many immature cells in various parts of infants brains as late as 2 years after birth.

Thate been struck with the close resemblance commented on also by Stevenson and Echlin between the structure of medulloblastomas and that of the

only in experienced hands, that even then mistakes can be made, and that all rapid diagnoses should be checked from properly prepared sections of fixed tissues

THE METASTASIS OF GLIOMAS

(1) Metastasis in the cerebrospinal spaces

This has already been referred to in Chapter 10. The frequent dissemination of medulloblastomas in the cranial and spinal meninges is now well known (Cairns and Russell. Wanke, and Fig. 402). Thecal dissemination from astrocytic gliomas has been recorded by Cairns and Russell, Russell and Cairns, and Eden. Intra-ventricular metastasis from oligodendroglioma was observed by Martin.

(2) Remote metastasis

Metastasis by the blood stream probably never takes place from gliomas I know of only three reported cases in which this is supposed to have occurred Davis (1928) saw a case which he regarded as a "spongioblastoma" of the brain with metastases in the left lung and in the soft ussues of the thoracic wall and arm, but the account is brief and incomplete, the illustrations are compatible with anaplastic carcinoma, and there is little doubt that a primary growth in the lung or some other part was overlooked. So also the tumour reported by Mittelbach (1934 and 1935) as a globlastoma" with metastases in the lungs was probably a primary bronchial carcinoma with a large cerebral metastasis. In a man of 28 years with a cerebelfar tumour diagnosed as an 'atypical medullo blastoma' (or possibly "sarcoma"), Nelson saw several discrete metastatic nodules in the vertebrae, all the viscera are said to have been clear, but the figures are not incompatible with anaplastic carcinoma.

GLIOMAS IN ANIMALS

Ghomas in animals are probably not as rare as the paucity of reports would suggest. Jungherr and Wolf reviewed a number of recorded cases in the dog, cat, ox horse, fowi and other birds, and they gave a good account of two astrocytomas in fowls. Belmonte also clearly described an astrocytoma in a fowl Schlotthauer and Kernohan described an astrocyting ghoma in a dog, and a tumour resembling human medulloblastoma was found in a 3 year old dog by Neubuerger and Davis. Ghomas appear to be excessively rare in rodents, the only possible instance. I have been able to discover is the cellular endothehoma' of the cerebrum found by Slye et al during their examination of over 11,000 brains of mice.

PINEALOMAS

Several kinds of tumours arise in the pineal gland—teratomas pinealomas, and occasionally true gliomas. The pinealomas, though not gliomas, are conveniently considered here. The pineal teratomas are discussed in Chapter 61

ventricle in young children and the other was from the pituitary region of a youth of 19

SOME SPECIAL FEATURES REGARDING THE STRUCTURE OF GLIOMAS

(1) Tissue culture of gliomas

Tissue culture has proved to be a valuable adjunct in studying the cytology of gliomas Buckley (1929) cultured multiform glioblastomas and found a close correspondence between the cellular characters in cultures and in sections of the growths including pleomorphism multinucleation and the formation of astrocyte like cells. Russell and Bland (1933 and 1934) confirmed this, and also found that the migrating cells in cultures of medulioblastoma oligodendroglioma and astrocytoma retained their specific characters. In cultures of multiform spongio blastomas cells resembling astrocytes were often produced, strongly supporting the view that these growths are anaplastic astrocytic tumours. Bailey s "unipolar spongioblastoma was proved by culture to be an astrocytoma. A cinematographic record of this work was made (Canti, Bland and Russell). Cox and Cranage also observed the migration of typical astrocytes from explants of astrocytoma in culture, and the migration of pleomorphic tumour cells from explants of gliobastomas.

(2) Calcification in gliomas

Almost any of the slowly growing kinds of intracranial tumours may calcify sometimes sufficiently to be visible in skingarians. This applies to meningiomas pituitary and parapituitary tumours pincal tumours, tumours of the chroid plexus haemangiomas and gliomas. The gliomas most prone to calcification are the oligodendrogliomas and the more chronic of the astrocytomas. The calcification sometimes appears first in the form of scattered spherules or irregularly in degenerated areas. but much more frequently it commences in the walls of blood vessels which finally become converted into completely calcified tubes as depicted by Bailey and Bucy and by Martin in oligodendrogliomas. This vascular or perivascular calcification sometimes involves also the vessels in the brain tissue peripheral to the tumour.

(3) Intranuclear inclusion bodies in gliomas

In astrocytic gliomas especially anaplastic ones, Russell (1932) frequently observed conspicuous intranuclear bodies resembling those often described as characteristic of virus infections. This observation should be taken not to suggest a virus causation for gliomas, but as a warning to virologists and others not to be misled by odd structural changes in tumour cells.

(4) Rapid diagnosis of gliomas by wet film smears and squashes

As Russell et al. (1937) have shown rapidly stained smears or squashes of fragments of tissue are capable of giving useful information as to the presence and nature of a tumour for the guidance of the surgeon during the operation I can confirm this from my own experience with a rapid haematoxylin-cosin method. But I think it important to emphasize that such methods are useful

due neither to destruction of the pineal gland nor to endocrine secretions of the pineal tumour cells, for precocity occurs with teratomas devoid of pineal elements (as in Horrax and Bailey's sixth case) and is in fact commoner with teraiomas than with pincalomas (Bochner and Scarff), and it may occur also with non pincal tumours of neighbouring parts (Le Marquand and Russell) It seems probable, then, that the precocity which may accompany pineal tumours is due to functional disturbance of neighbouring structures, especially the hypothalamus, or possibly to some constitutional peculiarity of the patients which also underlies the develop ment of the tumours

(4) Pinealomas in animals

The only record I know of is that of Schlotthauer and Kernohan, who saw a large pinealoma in a silver fox

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(1) Age and sex incidence

Most pinealomas occur in children adolescents or young adults cases over 30 years of age are exceptional Four out of 7 patients described by Globus and Silbert were under the age of puberty Males are much more often affected than femal s

(2) Structure and histogenesis

The structure usually regarded as characteristic consists of a mosaic of ill defined groups of large rounded cells bordered by zones of small darkly staining cells The former are regarded as pincal tumour cells proper but opinions differ as to the nature of the latter Bailey and Cushing and Bailey (1932) described these as connective tissue stroma containing lymphoid cells and Globus and Silbert also regarded them as young stromal cells which become fibroblasts These workers likened the pattern discernible clearly or vaguely in many pineal tumours to the distinct mosaic structure of the foetal and infantile pineal gland in which also they supposed the zones of small cells bordering the units of the mosaic to be young mesenchymal cells. This view, however is at variance with the opinions of most embryologists, and is moreover, refuted by Globus and Silbert's own excellent photographs of young pineal glands These show plainly that the small cells of the border zones of the foetal mosaic are not stromal but pineal parenchyma cells with all transitions to the larger central cells of the nodular areas In a genuine pinealoma then we may expect to find both large and small tumour cells with transitions between them an expectation which is realized in specimens like that depicted in Russell's figures 19 and 20 (1944) Horrax and Bailey's use of the name spongioblastoma 'in reference to poorly differentiated tumours of the pineal gland is confusing and has properly not been adopted

As Russell has pointed out confusion regarding the structure of pinealomas has been caused by including under this file some teratomas. Malignant teratomas of the pineal as well as those of the testis and other parts (see Chapter 61) often contain extensive areas of mosaie structure in which groups of large rounded embryonic cells are bordered by stroma with collections of lymphocytes. These areas may superficially resemble the mosaie areas of true pinealomas and it is this confusion of the two which has led to the idea that the small cells of pinealomas are lymphoid. Every pineal tumour must be very thoroughly and completely examined and until this is done on a sufficiently large series of specimens, uncertainty must remain regarding the relative frequency and properties of the two distinct kinds of pineal tumours pinealomas and teratomas. Russell may well be correct in her opinion that most pinealomas which have been reported hive probably been teratomas and that true pinealomas are much rarer. The whole subject of pineal tumours and their structure is in need of review especially by complete examination of the tumours and careful cytological study.

(3) Fndocrine disturbances associated with pineal tumours

Pineal tumours—either pinealomas or teratomas, occurring in young children have often been accompanied by precocious bodily—mental or sexual development (Horrax and Buley)—The explanation of this is still obscure—It appears to be

CHAPTER 53

PAPILLARY TUMOURS OF THE CHOROID PLEXUS

We are not concerned here with the rather common non neoplastic cystic and degenerative enlargements of the choroid plexus, which are often present in mild degree in middle aged and elderly subjects and occasionally large enough to produce symptoms. Most of the "psammomas" of the ventroles, including the large masses found in the ventricles of horses, are of this nature. True tumours of the choroid plexus are reported as papillomas or papillary carcinomas, but attempted separation into beingn and malignant growths is quite arbitrary and serves no useful purpose. One of the first clearly described cases was that of Douty (1886). The most useful recent accounts are those of Davis and Cushing Van Wagenen, Turner and Simon, and Posey. The following personally studied case illustrates most of the features of the disease.

Case I—Male aged 57 Histor—Weakness of legs atawa and falling to right side for 12 months. Examination disclosed nystagmits right lower facial paresis and defective sensation of right aide of face. Diagnosis cerebello pontine angle tumour. Operation partial removal of large firm but friable vascular tumour from this region patient died 3 days later from broncho pneumonia. Mecropy—Large residual mass of growth lay in cerebello pontine angle deeply indenting dorsal part of pons but projecting only slightly into dit wentrale. Scattered here and there on the surface of the spinal cord and spinal nerve roots there were several small white or grey nodules the largest millimeters in diameter. Except for pneumonia thoracic and abdominal organic were normal. Histology, (Figs. 404–405)—Well differentiated papillomatous growth closely resembling normal choroid plexus and showing much granular calcification. The implant nodules on the spinal cord are of similar structure.

(1) Age and sex incidence

Van Wagenen noted that the incidence of these growths is greatest in the first decade and declines with increasing age. The ages of 72 cases reviewed by Posey were as follows.

| Decades - | | ~ | - | 1 | : | 2 | } | 3 | 4 | 1 | 5 | 6 | 7 | 8 |
|-------------|---|---|-----|----|-----|---|---|----|---|---|----|---|---|---|
| No of cases | ~ | - | - ; | 27 | , , | , | 1 | 11 | 7 | 1 | 10 | 5 | 2 | 1 |
| | | | | | 1 | | | | } | | | , | | |

In one case the growth was found in a new born infant. Van Wagenen's first case was only 3 months old and Posey's case 6 months. The sexes appear to be about equally liable.

(2) Site

The fourth ventricle is the commonest site nearly 50 per cent of the growths arising here. Rather fewer tumours arise in the lateral ventricles and about 15 per cent in the third ventricle. Of 34 lateral ventricular tumours reviewed by Posey, 22 were left sided. It right sided and 1 bilateral. The almost completely

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irregular tumour filling and distending the left lateral and third ventricles

Microscopically, almost all of the growths are of fully differentiated plexus like structure, and calcified spherules like those of the normal plexus are often present, especially in adults. Turner and Simon, however, saw anaplastic features multinucleation and many mitores, in their two tumours, which they therefore regarded as being malignant. Needless to say, marked anaplasia in a supposed choroid plexus tumour demands consideration of the possibility of it being a metastasis of an unsuspected glandular careinoma elsewhere in the body, especially in the lungs, a possibility which only post mortem examination can eliminate

(4) Metastasis

Because of the benign micro structure and non invasive character of the growths, some writers have preferred to speak of 'seeding' rather than metastasis 'via the cerebrospinal fluid. This seems to me to be a distinction without a difference, for what is metastasis but successful transplantation of tumour fragments?

The following are good examples of the dissemination of plexus tumouts by the cerebrospinal fluid. Bielschowsky and Unger saw a papillary growth of the lateral recess of the fourth ventricle with multiple small implants on the basal meninges and cerebral cortex. From a tumour of the posterior horn of the lateral ventricle. Kono saw implants in the subarachnoid spices and on the cramal nerves. The papillary tumour of the fourth ventricle described by Toppisch had disseminated widely in the cramal and spinal meninges. Intraventricular implants were recorded by Van Wagenen (second case) and by Cairns and Russell. Schuster saw diffuse and nodular thickening of the cramal meninges, which was mistaken at first for tuberculous meningitis but which proved to be glandular carcinoma this may have arisen in the plexus of the third ventricle, but the possibility of metastasis from an undetected primary carcinoma elsewhere cannot be quite excluded. (See also Case I above and Fig. 405)

(5) Choroid plexus tumours in animals

The common 'cholesteatomas of the choroid plevus of old horses, a large bilateral specimen of which is depicted by Nieberle and Cohrs in their Fig 338, are not turmours but degenerative lessons. However prpillary turmours comparable with the human ones do occur in namials, e.g. the 'papillary adenoma of the ependyma' of the lateral ventricle of a mouse reported by Siye et al.

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extra ventricular position of the tumour in my case showed that it arose in the fringe of plexus which projects through Luschka's foramen



Fig. 404 - Case I Primary papillary growth of choroid plexus (× 75)

(3) Structure

The tumours are usually vascular friable visibly papillary and sometimes gritty from granular calcification. The extremes of size were exemplified by Van



Fig. 405 —Case 1 Metastasis on surface of spinal cord with calcified spherules (75)

Wagenen's two specimens—in one case a small well circumscribed tumour which was removed successfully from the lateral ventricle and in the other a huge

CHAPTER 54

NEURILEMMOMA AND OTHER TUMOURS OF NERVE-SHEATHS

THE PRINCIPAL subject of this Chapter is the specific Schwann cell tumour or neurilemmoma, but along with this we must consider also the less distinctive fibromas of nerves, for the two kinds of growth may occur together, and there is still uncertainty regarding the histogenesis of the several components of the nerve sheaths. Closer studies of their tumours will undoubtedly help to resolve this uncertainty

NEURILEMMOMA OR SCHWANN CELL TUMOUR

Masson's and Stout's names "Schwannoma' and "neurilemmoma', and Mallory's and Penfield's name' perneurnal fibroblastoma", express the two opposing views regarding the histogenesis of this distinctive nerve-sheath tumour. As the above heading indicates, I adhere to the former view, the structural evidence appears to me conclusive that this tumour indeed consists of neurilemmal cells. The frequently used name' neurinoma', introduced by Verocay, literally means nerve fibre tumour, and is therefore clearly inappropriate. The oaly really characteristic structural feature of neurilemmoma is the regimentation of its cells, the staining properties of its fibres are less distinctive.

(1) Age and sex incidence

(a) Age

The ages of Stout s 50 patients with neurilemmomas of peripheral nerves ranged from maney to 65 years, with no preponderance at any particular age period. Nielsen's 130 patients with acoustic nerve tumours ranged from 18 to 68 years of age on admission, the highest number being in the fourth decade and the average age being 42 (in Cushing's series it was 40) but the duration of symptoms before admission is not stated. I have examined 22 surgically removed acoustic tumours—the ages of the patients at the time of operation ranged from 17 to 65 13 of them were in the third and fourth decades, and the mean age was 37. The mean duration of symptoms was 32 months, the longest being 8 years in a man aged 51. The voungest patient, a girl aged 17, had had symptoms for one year. Following are the details of my 2 youngest cases of neurilemmoma of extra-cranial nerves.

Case I—A tumour which had been present for several years was removed from the 115 centimeters in main diameter. It was a smooth en-apsulated onoid mass 15 centimeters in main diameter. Histology—Typical neurilemmonts with all cells forming regular regimented groups and the fibres taking the usual stains for collagea (Fig. 406).

Case H—Routine skiagrams of the chest of a boy aged 17 about to enter the Navy showed the shadow of a rounded mass in the upper posterior mediastinium behind the root of one lung. This was removed successfully by $Mr \subset 1$ O. Brown of Melbourne It was an encapsulated mass 3 centimeters in diameter. composed parity of white tissue

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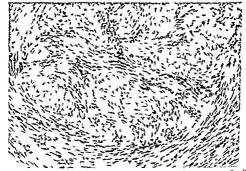
Turner O A and Simon M A (1937) Amer J Cancer 30 289

VAN WAGENEN, W P (1930) Papillomas of the choroid plexus Arch Surg 20 199
(A valuable review including details and figs of previously reported cases)

frequency of these tumours in the wall of the stomach is noteworthy. In this situation, confusion with myomas with regimented nuclei is easy, and indeed



Fir 407—Neurilemmont of parotid gland an encapsulated spherical tumour 1 centimeter in diameter from a young woman (Microscopically this was at first mistaken for a salivary adenoma of unusual type) (× 150)



F16 408 Neurslemmora of medulia of adrend gland a solitary lobulated tumour 8 millimetres in diameter found at necropsy on a min aged 51 (x 120)

I doubt if distinction is always possible (see Golden and Stout) Peptic ulceration may accompany the growth, as in a case reported by Fuller,

and partly of spongy vascular spaces Histology—Typical neurilemmoma with prominent regimentation of cells mixed with areas of cavernous vascular structure like that of an angioma

(b) Sex

Females appear to be more liable than males, e g 61 and 39 per cent respectively in Nielsen s series of acoustic tumours, and 64 and 36 per cent in Cushing s series My 22 specimens of acoustic tumour came from 15 women and 7 men Stout s 50 patients with peripheral tumours comprised 28 females and 22 males

(2) Site

(a) Intracranial nerves

The acoustic nerve is the commonest single site and most of the tumours arise in or near the internal meatus. In routine sections of temporal bones Hardy

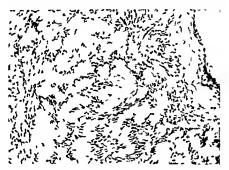


Fig 406 -- Case I Neurslemmoma of tongue (× 150)

and Crowe discovered several examples of tiny symptomiess tumours of the auditory nerve deep in the canal. Other cranial nerves are rarely the site of neurifemmonis. Kovács saw a solitary tumour of this kind on the oculomotor nerve. Krayenbuhl reviewed the primary tumours of the trigeminal nerve and Gasserian ginglion. no doubt some of these are neurilemmonias similar to the nuditory nerve tumours.

(b) Peripheral nerves

Stout's review of peripheral neurilemmomas showed these to occur most frequently on main nerves on the flexor aspects of the limbs in the hands neek, scalp face tongue and stomach the trink was an infrequent site and no tumours were seen in the feet urogenital organs lungs oesophagus or rectum. The

frequency of these tumours in the wall of the stomach is noteworthy. In this situation, confusion with myomas with regimented nuclei is easy, and indeed

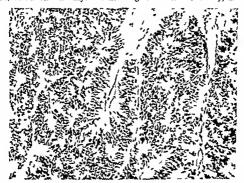


Fig. 407—Neurilemmoma of parotid gland an encapsulated spherical tumour 1 centimetre in diameter from a young woman (Microscopically this was at first mistaken for a salivary adenoma of unusual type) (x 150)

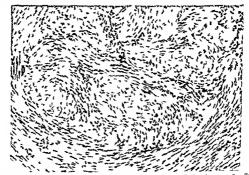


Fig. 408 Neurilemmoma of medulia of adrenal gland a solitary lobulated tumour 8 millimetres in diameter found at necropsy on a man aged 51 (x 120)

I doubt if distinction is always possible (see Golden and Stout) Peptic ulceration may accompany the growth, as in a case reported by Fuller,

and in a similar specimen which I examined. Other sites of neurilemmomas in my series included the tongue (Case I), parotid gland (Fig. 407) the posterior



Fig. 409 —From the same specimen as Fig. 408 showing two nerve cells included within the whorled regimented tumour tissue $(\times 350)$

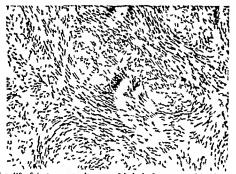


Fig. 410 -- Subcutaneous neurstemmoma of the back of a woman aged 45 (× 120)

mediastinum (Case II) the sealp (Case III below) the intestine (Case VII below) the medulla of the adrenal gland (Figs. 409 409) the subcutaneous tissue of the back (Figs. 410 411) and the spinal theca (Fig. 412)

(3) Number of tumours, and concomitant lesions

In most cases, structurally typical neurilemmomas are solitary growths unaccompanied by signs of neurofibromatosis or other lesions of the nervous system. In a minority of cases, however, the tumours are multiple or are accompanied by neurofibromatosis or by minor stigmata of that disease. This applied to 9 of Stout's 50 cases. Generalized neurofibromatosis may include bilateral acoustic tumours, as in Gray a cases, and bilateral acoustic tumours are sometimes the principal manifestation of familial neurofibromatosis (Gardner and Turner). My personally studied cases of neurilemmoma included one

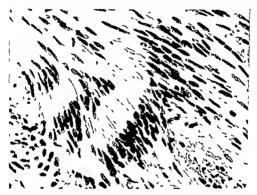


Fig 411 -Detail of Fig 410 (x 400)

showing 3 separate tumours in the wall of the small intestine in \(\tau\) woman aged 58 another of multiple intestinal tumours in a woman aged 47 with neuro fibromatosis (Case VII below) and the following case with 2 tumours

Case III —For years a woman aged 45 had noticed 2 small rounded sub-utaneous tumours one of the neck and one of the scalp. These were diagnosed sebaceous cysts and were excised. They proved to be solid tumours microscopically typically regimented neutrilemnomas.

The presence of a neurilemmoma therefore calls for careful search for tumours of nerves in other parts of the body, but in most cases none will be found

(4) Structure

(a) Naked eye appearance

A neurilemmoma is well circumscribed and often encapsulated, and, if it arises from a large nerve, it shows the intact nerve bundles passing to one side of it or spread out over its surface. Most tumours are rounded or ovoid but

and in a similar specimen which I examined Other sites of neurilemmomas in my series included the tongue (Case I) parotid gland (Fig 407), the posterior



Fig. 409 —From the same specimen as Fig. 403 showing two nerve cells included within the whorled regimented tumour tissue. (× 350)

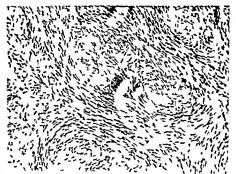


Fig. 410 —Subcutaneous neurilemmoma of the back of a woman aged 45 (× 120)

mediastinum (Case II) the sealp (Case III below) the intestine (Case VII below), the medulia of the adrenal gland (Figs 408 409) the subcutaneous tissue of the back (Figs 410 411) and the spinal theea (Fig 412)

in which regimentation is scanty or indefinite are indistinguishable from ordinary fibromas

- (11) Reticular or so-called "type B" tissue shows a disorderly loose meshwork of cells of variable shapes, often with plentiful intercellular vacuoles or microcysts containing watery or mucinoid fluid which stains bluish with haematovylin Regimented cells and parallel fibre-bundles are not found, and indeed collagen fibres are scanty or absent Type A and type B tissues are often present together, they are continuous with one another, but their junctions are usually abrupt
- (iii) A third type of structure, the epithelioid, is less frequently described. It shows closely aggregated plump cells with scanty intercellular spaces and fibres or with none. Over small areas this superficially resembles an epithelial structure, but elsewhere it passes into the fasciculated or reticular type of growth. I have seen this rather misleading type of structure in only two tumours, both from the stomach.

Nerve fibres are rarely to be found in the substance of the tumour, they he outside the capsule, or at the most a few residual fibres may be found just within its margins.

Gross degenerative changes are unusual, but collections of lipoid laden foam cells are sometimes present, especially in acoustic nerve tumours

(5) Growth and behaviour

Neurilemmomas grow slowly remain well circumscribed and are readily cured by local removal. When the tumour myolves a large nerve, it is usually unnecessary to excise the nerve, careful stripping of the nerve bundles from the surface of the growth will usually permit its enucleation. A tumour which cannot be enucleated because it involves a nerve diffusely and without encapsulation is not a neurilemmoma. Recurrence of a neurilemmoma may of course take place in situations where complete removal is not practicable as in the certbello pontine angle, but measily accessible peripheral sites, enucleation has rarely been followed by recurrence Malignant properties, infiltration and metastasis, are said never to occur (Stout), but in my opinion an open mind is still called for on this point. Is it not possible, even probable that malignant properties might be accompanied by loss of nuclear regimentation and other structural features on which the recognition of a neurilemmoma depends? In the following case an invasive malignant growth, diagnosed microscopically "neurogenic sarcoma", showed distinct regimentation in parts Is it a neurogenic fibrosarcoma which happens to show regimentation or an invasive neurilemmoma, or a combination of both?

Case IV—For 2 years a woman aged 47 had noticed an increasing mass in the subcutaneous tissue of the abdominal wall below the navel Recently this had grown more rapidly and some small satellite growths had developed around it. It was excised along with the overlying skin. The main mass was rounded 3 centimeters in diameter well defined but was connected by strand like outrunners with 4 smaller adjacent nodules all composed of firm white fasciculated tissue. Though not adherent to these growths the skin overlying them showed irregular white thickening of the detimis over an area 3 centimeters in diameter. Histology—Moderately cellular whorled and fasciculated spindle-celled growth well circumscribed in some places but diffusely infiltrating the subcutaneous tissue and dermis in others. Prominent regimentation of the cells is

the tumour depicted in Figs 410 and 411 was an elongated tortuous cylindrical growth 65 centimetres long and 18 centimetres in diameter. The tumour tissue is usually of uniform texture, soft or moderately firm in consistency, and pink, grey or yellowish in colour Large tumours sometimes show some hydropic or cystic change

(b) The microscopic structure

The following rather distinct but of course not sharply separable patterns are encountered

(i) Fasciculated or so called 'type A' tissue is the most characteristic often enabling the tumour to be identified at a glance. It shows an orderly arrangement

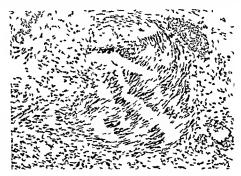


Fig. 412 —Intrathecal neurilemmoma from a woman aged 55 (× 120)

of parallel cells and intercellular fibres, forming interwoven bundles. In these the cells often he in transverse parallel ranks separated by nucleus free zones of densely aggregated fibres along with the terminal portions of the cells alternation of fibrous and nucleur zones gives the distinctive palisaded or regi mented pattern. The regimentation may be in simple parallel bands or may take sinuous or complicated forms. Masson drew attention to the close re-em blance of the structure of palisaded tumour nodules to that of the neurilemmal supporting elements of Wagner Meissner tactile corpuseles and supported this comparison with some convincing photographs. Distinct regimentation is not always present or it may be so scanty that it must be sought for. The neurilem moma fibres consist of a form of reticulin or collagen which however stains somewhat differently from fibroblastic collagen. With Van Gieson's stain it often assumes varying tints of yellow orange and brown but in old dense tumours it stains red or pink like mesenchymal collagen. Old collagenous neurilemmomas

unchanged Does it not indicate that what we class under the general term of connective tissue is not uniform either in structure or function, but in each organ or system may have its own special endowment?"

(1) Personally studied cases

The following personally studied cases of neurofibromatosis exemplify many of the features of the disease

Case V-Male aged 40. A pale wirened bent man appearing much older than his age had 10 brothers and sisters all healthy and there was no record of similar disease.

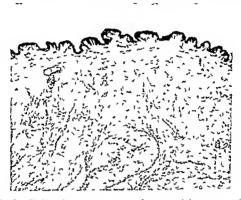


Fig. 414—Case V. Neurofibromatous thickening of dermis including a nerve with great thickening of its sheath. (x 18)

in any other near relatives. The patient had fundreds of small painless skin tumours on his trunk limbs and neck, with patienty pigmentation of the skin. These had been present since childhood and had grown only slightly. The largest growth in one thigh had increased in size from a diameter of 5 centimetres when he was 28 years old to 6.5 centimetres 12 years later. This tumour and a smaller adjacent one were excised microscopically they were soft semi translucent fairly well defined massis. Upical being neurofibromata of only moderate cellularity, with no regimentation and with recognizable nerve fibres traversing the whorled libroblastic tissue in places (Fig. 414).

Case VI—Male aged 35 with no family history of neurofibromatosis had had a swelling in the right side of the neck since childhood without any increase in size in recent years. Recently he had noticed atrophy of right thener bilateral deaffixes and some headaches. Examination showed a large diffuse firm swelling in the right upper neck with small extensions in the lower part of the neck an ill defined nodular mass 3 centimetres in diameter in the right axilla a well defined subcutaneous mass 2 centimetre in diameter in the outer aspect of left thigh a small projecting nodule on the back of the scalp many pigmented patches on the skin of the trunk slight bilateral propiosis of

Present in parts especially where the growth infiltrates adipose tissue (Fig. 413). The intercellular matrix is partly colfagenous and fibrous and partly mucinous. Mitotic figures are few even in poorty differentiated cellular areas.

NEUROFIBROMATOSIS

I do not propose to give a detailed account of the protean manifestations of this disease. From an enormous literature I suggest the following papers for useful descriptions, reviews and sources of reference on visceral neurofibro matosis. Banatjee and Christeller Grill and Kuzma, Barton and Inglis, Meyer,

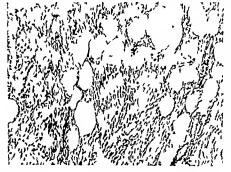


Fig. 413—Case 11 Malignant neurilemmoma of abdominal wall showing regimented cells infiltrating subcutaneous adipose tissue (× 120)

on the association of neurofibromatosis with tumours or other lessons of the brain, spinal cord and meninges. Harbitz Martz Schairer. Scherer Worster Drought et al. Turner and Gardner or with tumours of the optic nerve or its sheaths. Davis on the hereditary character of neurofibromatosis. Gardner and Turner Turner and Gardner. Grill and Kuzma on histogenesis. Schierer Turner and Gardner, Bailey and Herrmann and on sarcomatous change. Stewart and Copelind. (see also below). Neurofibromatosis may also be associated with pigmented moles. (Chapter 58). with hipomas. (Chapter 42). with chromoffine tumours (Rosenthal and Willis) with rhabdomyosarcomas (Masson and Martin) or with craino facial or other malformations (Weber and Bode. Grill and Kuzma and other references by Stewart and Copeland). Muller described congenital neurofibromations macroglossia. Good descriptions of pleuform neurofibro matosis include those of De Morgan and Coupland and Plengs. The following comment of the former made in 1875 is worth citing. It is an interesting pathological faet that we may have a disposition to new growths pervading extensively the connective tissue of nerve alone while all other parts of the body remain

or involves nerves diffusely for variable distances. Nerve fibres are often to be found traversing the tumours. Whorfs and fasciculi in the growth often clearly follow patterns determined by the inclusion of neurofibromatous nerve bundles within it. It is as if the entire nerve has suffered expansion, with separation of all its constituent fibres by a universal diffuse increase of all its sheath tissues. The general structure and staining properties of the bulk of the tissue are usually similar to those of mesenchymal fibrous or mucoid tissue, but in some tumours or parts of tumours the staining properties of the fibres are indefinite and not characteristic of collagen. Definite Schwann cells of the iffected nerves can often be recognized in the growths, but it is often impossible to identify individual cells as either Schwannian or fibroblastic. Many workers have concluded that the bulk of the neurofibromatous tissues is endoneurial or permeural and fibroblastic (eg. Bailey and Herrmann), others that it is mainly Schwannian (eg. Stewart and Copeland).

That Schwann cells do participate in the tumours in generalized neurofibro matois is shown by cases like Nos VI and VII above, in which characteristic regimentation was found in one or more tumours. Reference has already been made also to Stout's finding that some cases of neurofibromatosis, and to the occurrence of acoustic neurilemmomas in cases of teneralized neurofibromatosis.

or generalized feuronoromatosis

(3) Sarcomatous change in neurofibromatosis

The proneness of the lessons of neurofibromatosis to sarcomatous change halong been recognized One of the earliest reports was that of Coupland and Balding (1877) who, in a patient with multiple subcutaneous fibromas, saw 4 myxosarcoma of the sciatic nerve with pleural and mediastinal metastases. Other noteworthy reports and reviews include those of Westphalen, de Santi, Hartman, Quick and Cutler Plenge Lewis and Hart, Hosoi, and Stewart and Copeland (See also Case VII above).

The structure of the malignant growths is very variable. Many contain mysosarcoma like areas, some resemble fibrovarcomas and others are highly cellular spindle celled or pleomorphic-celled growths. Large compact masses or smaller groups of plump polyhedral cells are not uncommon, giving parts of the tumours a resemblance to anaplastic carcinoma. Of course, these characters afford little or no reliable evidence regarding the histogenesis of the neurofibromas but, as a group neurogenic sarcomas are rather different from the ordinary sarcomas of non neural mesenchymal tissues.

(4) General comments on neurofibromatosis

(i) In spite of the great diversity of its clinical appearances, neurofibromatosis is one disease. Multiple, cutaneous or visceral growths, diffuse plexiform growths, neurofibromatous elephantiasis of limbs or other parts, are all manifestations of a similar change.

(ii) Most of the benign lesions of neurofibromatosis are not true tumours but tumour like developmental anomalies or hamartomas. In many cases the growths remain stationary or increase in size only slowly over a period of many

the eyes and marked deafness. The thigh tumour was excised microscopically it showed whorled areas synide-celled areas with regimented cells much loose poorly cellular connective issue and some cystic spaces.

Case VII—Female aged 47 Since childhood skin of trunk and limbs had been covered with hundreds of small sessile timmour. For last few months she had suffered from pain in left thigh weakness and an increasing abdominal mass. Accropsi—Retropersonceal tumour 33 centimeters in diameter extended from lower pole of left kidney to pelvis adherent to vertebrae and to intestine on section tough fibrous with degenerated areas and cysts. Multiple well-defined white fasciculated tumours were

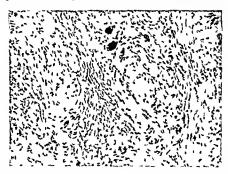


Fig. 415—Case VII Neurofibroma of small intestine with included nerve cells of Auerbach a plexus (× 80)

present in wall of small intestine the largest 4 centimetres in diameter—other viscera unaffected—Histology—Large tumour—spindle-cell fibrosarcoma—Small tumours whorled and fasciculated benign spindle-celled growths, with slight regimentation in parts and with included cells of Auerbach's plexus (Fig. 415)

Case VIII (Reported by Rosenthal and Willis)—Male aged 52 Necrops)—Many small cutareous neurofibromata devoid of regimentation bilateral chromaffin-cell tumours of the adrenals fatal pulmonary tuberculosis.

These cases severally illustrate the not unusual absence of a family history of the disease the frequently long duration of the tumours with little or no increase in size the sporadic distribution of tumours in some cases multiple intestinal tumours associated chromaffin tumours the usual absence of microscopical evidence of the presence of Schwann cells but on the other hand the occasional presence of regimentation (Cases VI and VII) and the supervention of sarcoma

(2) Structure of neurofibromala

In most cases the structure of the multiple growths of neurofibromatosis is unlike that of the solitary neurolemmoma. The turnour tissue is not well-circum seribed or encapsulated but mingles with the surrounding dermal or other tissues.

regimented growths with fibres staining quite unlike collagen and densely collagenous growths resembling ordinary fibromas. This demonstrable collagen forming property of Schwann cells at once impels attention to the possibility, suggested by Masson, that the supposedly fibroblastic endoneurium and per neurium may be of neurolemmal origin or at least may contain neurolemmal elements. Or, granting that the components of nerve sheaths may come from two distinct sources, perhaps they form a unified system, in which germ layer distinctions have little meaning and in which there is a gradation of cell properties, from those of the distinctive Schwann cells in immediate contact with the nerve fibre to those of the non distinctive fibroblasts of the epineurium and perineurium remote from the nerve fibre.

In taking this view we would abandon sharp distinction between the supposedly ectodermal and mesenchymal constituents of nerve-sheaths and would regard the properties of particular cells as determined by their positions in the nerves and not by their germ layer origin. Adoption of this view would largely resolve the difficulties in interpreting the structure of nerve sheath tumours. According to it, we might expect to encounter tumours of distinctive Schwann cell type, others of non distinctive mesenchymal type, and others of associated, combined or transitional type. And this, in fact, is what we find

NEURO EPITHELIAL TUMOURS OF NERVES

None of the few reports of supposedly primary epithelial tumours of nerves is acceptable. Stout (1918) described a patient with large tumours in the axilla and in the course of the ulnar nerve, composed of masses of epithelium like tissue containing rosettes said to resemble those of retinoblastoma. In the absence of follow up and necropsy findings, it is impossible to exclude the possibility of a primary carcinoma of the lungs or of some other organ in this case Cohn reported the case of a man with a carcinomatous tumour of the cubital fossa involving the radial nerve, and although necro psy disclosed a large carcinoma of the right lung and metastases in many other organs, Cohn inclined to the clearly erroneous view that the cubital tumour was a primary epithelial growth of the radial nerve Under the title 'malignant neurinoma with epithelial elements", Brandes described a large tumour of the thigh in an old man this was spindle celled but contained epithelial clumps, and epithelial metastases were found in lymph glands and lungs Brandes stated that no other primary growth was found, but failed to mention the stomach pancreas, thyroid and several other epithelial organs Stout (1935) reviewed the reported cases of sup posedly primary epithelial tumours of nerves and accepted 3 of them, but noted that they all differed in structure Stout and Murray reported as neuro epithelioma' an anaplastic tumour of the radial nerve in a man aged 35, who later developed tumours in both lungs as revealed by radiographic evidence, the figures show a pleomorphic celled tumour without distinct epithelial characters. In my opinion none of the cases cited was of indubitable nature Unless very thorough necropsy is performed in such cases the possibility of the nerve tumours being metastatic cannot be excluded Moreover, it must not be forgotten that compact

years or throughout life. The underlying developmental error is genetic at least in part and though its main effects are visited on nerve sheaths the development of other parts of the nervous system and its envelopes may also be disturbed

(11) The development of neurilemmoma of localized progressive fibroma or of neurogenic sarcoma, must be looked upon as a supervention on the original

lesion, a supervention to which, however, it is strongly predisposed

SOLITARY NEUROFIBROMA AND NEUROGENIC SARCOMA

Solitary neurofibromas and neurogenic sarcomas, structurally similar to those of you Recklinghausen's disease, but unaccompanied by any signs of that disease, are relatively common. My own experience includes a benign neuro fibroms of the radial nerve in a man need 21, a small neurofibroms of the oculo motor nerve (reported by Elder) a neurogenic sarcoma of the peroneal nerve of a woman aged 27 and the following case of sarcoma of the radial nerve

Case IX -History -A man aged 22 noticed a painful rapidly enlarging swelling in his right cubital fossa. This was diagnosed abscess, and was incised but no pus was found Biopsy showed rapidly growing spindle-celled sarcoma. Amputation above the elbow was performed and dissection and microscopical examination showed the tumour to extend diffusely along the radial nerve and to invade neighbouring veins. Death occurred one year later. Accropsy showed multiple metastases in both lungs several bones reiroperatoneal tissues pelvic lymph glands scalp and medulla of left adrenal Histology-All tumours showed diffusely infiltrating pleomorphic-celled growth with some distinctly myxosarcomatous areas

HISTOGENESIS OF TUMOURS OF NERVE SHEATHS

From the foregoing account the following conclusions emerge

(i) There occurs a distinctive nerve sheath tumour, usually solitary and benign the structure of which shows (conclusively, I think) its derivation solely from the neurslemmal cells of Schwann, and which therefore is appropriately called neurilemmoma?

(ii) Most of the lesions of generalized neurofibromatosis do not show this structure but neurilemmomas may develop in cases of this disease

(iii) Benign nerve sheath tumours resembling those of neurofibromatosis and devoid of distinctive neurilemmoma structure also occur as solitary

(iv) Malignant growths occur as isolated lesions or in cases of neurolibroma these rarely show any evidence of neutrlemmomatous structure but occasionally they do so

Correct concepts of the histogenesis of nerve sheath tumours are of course dependent on correct concepts of the histogenesis of the nerve sheaths themselves The most widely recepted view has been that the Schwann cells are special ecto dermal derivatives of the neural crest and are to be distinguished sharply from the mesenchymal fibroblasts of the endoneurium and perineurium. Studies of the proliferation of Schwann cells in injured nerves and in vitro (Masson, Murray and Stout Murray Stout and Bradley) while showing that these eells probably do possess distinctive characters not shared by mesenchymal cells have shown too that Schwann cells can form collagen This property is clear also from the structure of neurilemmomas in which all gradations can be traced between typically

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polyhedral celled areas of neurogenic sarcomas may simulate anaplastic epithelial growth, but this appearance does not warrant calling the tumour 'epithelial'

TUMOURS OF NERVES IN ANIMALS

Multiple dermal fibromata apparently comparable with human neurofibro matosis, have been described in the horse, dog and deer (Feldman), and Nieberle and Cohrs described and depicted multiple diffuse neurofibromata of the axiliary plexus, sympathetic nerves and heart in the ox Some solitary libromas and fibrosarcomas in animals also show structural evidence of origin from nerve sheaths. Young and Olafson saw multiple nerve sheath fibromas in a family of brook trout these tumours had a whorled structure but no nuclear regimentation, so that the authors diagnosis of neurilemmoma is question able. Lucke however, saw undoubted neurilemmomas in 76 adult fish belonging to 3 species of snappers, 65 of the fish had solitary tumours 7 had 2 tumours and 4 had more than 2 tumours each. Nelson et al observed neurilemmomas of the ears of ratis which had been fed for long periods with crude ergot

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Murray M R and Stout A P (1947) Anat Rec 84 275

respectively The tumours described by Moore (1885) and Chaffey (1885) also were undoubtedly adrenal neuroblastomas Dalton's case (1885) of 'infil trating growth in liver and suprarenal' in an infant 6 weeks old is of special interest, because Dalton clearly described and depicted the characteristic arrange ment of cells in rosettes in the adrenal tumour, and because in spite of the great size of the hepatic growth as compared with that in the adrenal he suspected the tumour of "originating in the medulla of this organ. The liver affection might then be secondary." An admirable example of scientific caution which some modern writers in this field would do well to emulate!

In spite of correct identification of the nature of the tumours by Marchand in 1891, the erroneous view that they were sarcomas persisted well into the present century. In 1901 Pepper described as "congenital sarcoma of the liver and suprarenal the syndrome of massive hepatic metastasis from adrenal neuro blastoma, which is now often called "Pepper's syndrome." In 1907, Hutchison laid emphasis on the syndrome of 'suprarenal sarcoma in children with metastases in the skull.", he suggested that some of the tumours may have been, not sarcomas, but "malignant hypernephromata", but he did not mention their possible neural origin. So also Tileston and Wolbach (1908), though they observed cell rosettes in a tumour which had produced Hutchison's syndrome, failed to appreciate their significance.

The view of Ribbert and his school that the tumours were 'gliomas' had a deservedly short life. As examples of cases reported as such may be mentioned those of Kuster (1905) and Schilder (1909). Kuster's report is of interest in that in her first case bilateral adrenal tumours were present in an infant 14 weeks old and in her second case the subject was an adult, while Schilder's case was that of an infant only 7 days old with a tumour of the abdominal sympathetic chain. In both Kuster's and Schilder's cases the tumours contained prominent rosettes.

The true nature of the tumours was first recognized in 1891 by Marchand, who likened the tissue of the tumours to that of the developing sympathetic ganglia. This view was more clearly stated by Wresel (1905) who strongly criticized Kuster's identification of the rosettes as gliomatous, and insisted on their identity with the 'Markballen' of the embryonic adrenal medulia or sympathetic ganglia (see Fig 416). Wiesel also noted that such groups of sympathetic formative cells may be found in the adrenals as late as puberty. A most important paper which finally established the identity of the neuro blastomas was that of Wright (1910) who reviewed previous records, reported several new cases, and gave some beautiful photographs comparing the rosettes and parallel bundles of fibrils seen in the tumours with those seen in embryonic adrenal medulia and sympathetic system. One of Wright's cases was a still born male infant with tumours in both adrenals.

Subsequent contributions of importance include those of Herxheimer and Wahl in 1914. Herxheimer using the Bielschowsky method gave proof for the first time that the fibrils in an adrenal neuroblastoma were fine nerve fibres. His specimen also afforded proof that the fibres arose as out growths of the cells and were not formed by sheath cells, since unlike the well differentiated ganglioneuromas the tumour contained no sheath cells, ic the

CHAPTER 55

NEUROBLASTOMA AND GANGLIONEUROMA

By NEUROBLASTOMA is meant a tumour consisting of immature undifferentiated neuroblasts, and by ganglioneuroma is meant one consisting of well differentiated nerve cells and fibres. The two types of growth are not sharply distinct however, many tumours of transitional or mixed structure occur and the two names denote merely the poorly differentiated and the highly differentiated members of the same species, the former rapidly growing and malignant the latter slowly growing and relatively benign. All intermediate gradations of structure and behaviour are observed. Hence while in the several sections of this chapter it will be convenient for descriptive purposes to consider separately the two main types of growth the unity of the entire group of tumours must never be lost sight of

Contrary to what we might have anticipated, these nerve cell tumours are extremely rare (if indeed they ever occur) in the central nervous system while their most frequent sites of origin are the adrenal glands and the ganglia of the sympathetic system. Although they sometimes appear first in indult life, they are much more frequent in infancy and childhood indeed rivilling the embryonic tumours of the kidney as the commonest form of malignant neoplasm in children. The structure of the incompletely differentiated tumours of this group resembles that of the immature tissue of developing sympathetic ganglia and recognition of this similarity was an important step in our knowledge of the histogenesis of these tumours.

HISTORICAL OUTLINE

(1) Neuroblastoma

The history of the imperfectly differentiated neuroblastomas shows three periods in the first period the tumours were called sarcomas" in the second period they were regarded as of glial nature and finally their true nerve-cell character was recognized

Although in the first period the specific nature of the tumour cells as sympathetic formative cells was not known and the tumours were regarded as found celled sarcomas or lymphostreomas many of the early recorded tumours are readily recognizable. Possibly neuroblastomatous was the tumour described by Morgan (1879) as sarcoma of the scapula in an infant 9 weeks old the left adrenal as well as other viscera contained growth and the sarcomatous tissue showed some parts delicately fibrillated was the tumour reported by Abererombic (1880) as 'multiple sarcomation of cranial bones in a female child aged 4 there was a tumour beneath the left adrenal accompanied by a chain of involved lumbar lymph glands and multiple deposits in other parts of the skeleton as well as the skull. So vlso Parker's case (1880) of congenital sarcoma of the liver was clearly one of adrenal neuroblastoma with secondary disease of the liver. Abererombic s and Parker's cases are the first records of the syndromes litter described by Hutchison and Papper.

"sympathicoblastoma", "sympathogonionoma", "gangliosympathicoblastoma" All of these names are correct enough, but of course do not denote different tumours Rigid classification and nomenclature are impossible hecause of the wide range of differentiation in different tumours or even in one tumour, as particularly insisted on by Wahl, Robertson, and Blacklock (1934) The only valid objection to the simple name neuroblastoma" for the entire group of imperfectly differ entiated tumours is that, as Wahl's case showed, the tumour cells may sometimes display their potentiality for differentiating into chromaffin cells as well as nerve This, however, is a very trifling defect, which the other names mentioned ahove do not remedy, and Wahl himself considered "neurohlastoma simplest and best name. It may be added here that the number of tumours in which, like Wahl's, chromaffin cell potency is displayed is very small, in the great majority of cases any differentiation displayed is in the direction of the formation of neurones only, ie the cells are potential neuroblasts, and the name "neuro blastoma" is unreservedly applicable. The occasional cases in which some of the cells show a supplementary direction of differentiation do not justify additional names

(2) Ganglioneuroma

Correct identification of nerve cell tumours was of course made first with the well differentiated growths containing easily recognizable nerve cells Prior to Virchow's classical work on tumours (1863–1867), the term "neuroma' had been applied to all new growths arising from nerves, most of which were of course tumours of the nerve-sheaths Virchow proposed a distinction between these false neuromas" and "true neuromas" composed of nervous elements proper A true neuroma containing nerve cells Virchow proposed to call "neuroma gangliocellulare", though no proven case of this kind had so far been described

The first clear instance of a nerve cell tumour justifying Virchow's prophetic terminology was that described in 1870 by Loretz, an encapsulated growth of the thoracic sympathetic chain in a woman of 35 years containing well formed unipolar nerve cells and non medullated nerve fibres. This was followed in 1879 by Key's account (inaccessible to me) of a ganglioneuroma of the nose in a man aged 31 years, presumed to have arisen from the infra orbital nerve, and by Weichselbaum's report (1881) of a small well defined ganglioneuroma of the medulla of the adrenal gland in a man aged 76 years. No cases were reported for the next 18 years, until 1898, when Busse described a huge retropertioneal ganglioneuroma in a boy aged 4 years

From then on there appeared an increasing number of reported examples of ganghoneuroma, the favourite sites of origin of which were soon recognized to be the sympathetic system and adrenal glands. These were fully reviewed in the papers of Beneke (1901) and Wegelin (1909). An unusual case was that described by Knauss in 1898. A female child aged 3 had many widespread subcutaneous tumours consisting of non medullated and a few medullated nerve fihres and many nerve cells. Knauss found the tumours to be related to small arteries and believed them to have arisen from the perivascular sympathetic plexises. A similar case was described in 1902 by Beneke and Kredel (cited by Herxheimer)

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formation of nerve fibres precedes the development of sheath cells in these neural tumours. Another paper of note was by Landau (1912) who gave a thorough review, added three typical examples (one with bilateral adrenal growths and hepatic metastases in a new born infant), noted the range of structural differ entiation in this group of tumours and its correspondence with their degree of malignancy and suggested that the cluef period of sympathetic differentiation in late foetal and early post natal life accords well with the time of origin of the tumours and points to their dysontogenetic nature. Robertson's paper (1915) stressed the occurrence of all combinations of, and transitions between, well

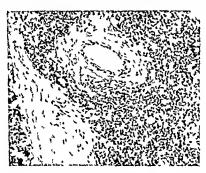


Fig. 416 - Coeliac ganglion of 4 months human foctus showing neuroblastic rosettes (v 125)

differentiated ganglioneutomas and undifferentiated neuroblastomas. Blumensaat (1938) drew special attention to the occasional appearance of neuroblastomas in adults (although Blumensaat's own report is not completely contineing probably owing to the long interval of 48 hours after death before the miterial was obtained). Bulbring (1928) and Rinscheid (1936) confirmed Herxheimer's earlier finding of the specific staining properties of the young nerve fibres in neuroblastomas—the second worker observing in the tumour cells themselves a fine silver stainable fibrillary network resembling that seen in normal neuroblasts and stressing the variable degree of neurone differentiation to be seen in these tumours.

Nomenclature

Various workers have proposed elaborate schemes of classification and nomenclature for the turnours according to their degree of differentiation. In addition to neuroblastoma and neurocytoma other names which have been used include the following sympathoma embryonale

ganglioneuroma, of weight 1,020 grammes, successfully removed from a woman aged 27, and Cappell's excellent account is accompanied by particularly beautiful microphotographs

(1) Neuroblastomas AGE INCIDENCE

On the average, neuroblastomas make their appearance decidedly earlier than ganglioneuromas. Collected records (see for example, Scott et al., 1933) show that in about one half of reported cases the patients have been less than 2 years old, and at least three quarters of them less than 4 years. In some cases the tumours are known to have been present at birth, even causing dystoma Wells (1940) has given an excellent review of congenital neuroblastomas, which includes those of Dalton Richards, Wright, Landau, Fischer, Hagstrom and Rinscheid, as well as 4 cases described by Wells himself

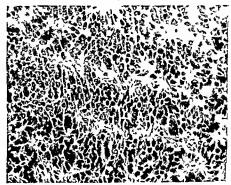


Fig. 417—From pulmonary metastases of a primary neuroblastoma of the coeliae ganglion in a man aged 51 showing cells in rosettes and wavy parallel zones with intervening fibrils (Dr Leila M Hawkile) s specimen from Cancer Hospital London) (× 340)

However, the exact age distribution is still uncertain because the occurrence of adolescent and adult cases has been clearly recognized only within recent years, and such cases are still being misdiagnosed by both clinicians and pathologists e.g. as 'Ewing's tumour' (see below). The earlier reviewers of the subject, e.g. Landau and Herkheimer, believed neuroblastomas to occur only in childhood, and the clinical prominence of the striking syndromes first described by Pepper and Hutchison undoubtedly led to overestimation of the frequency of the earlier appearing tumours of this class. A correct estimate of the age distribution of neuroblastomas will be possible only when clinicians and pathologists are much wider awake to the occurrence of adult cases like those reviewed by Blumensaat and like that depicted in Figs. 417 and 418 and are much less prone to mis identification of adult and adolescent crises as indicated in my 1940 paper on

A case described by Bruchanow in 1899 resembled Weichselbaum's case in that the tumour was a small well defined nodule in the adrenal gland in an elderly person a woman aged 65 In 1901 Beneke gave a detailed account of 2 carefully studied ganglioneuromas. In the first case one of pelvic ganglioneuroma in a woman aged 25 Beneke noted all transitions between small and large nerve cells observed that the younger cells were aggregated in groups which he regarded as centres of proliferation commented on the frequent presence of multiple nuclei in the cells and concluded that the ganglion cells were the essential neoplastic element in the growth that the nerve fibres were produced by the cells and that the abundant Schwann cells constituted an accompanying stroma to the fibres Beneke s second ease a large retroperatoneal turnour in a girl aged 10 was the first reported instance of a malignant ganglioneuroma with metastases bulk of the growth consisted of well differentiated ganglioneuromatous tissue but some areas presented small poorly differentiated cells devoid of fibres and a metastatie deposit in an adjacent lymph gland had a similar undifferentiated structure. Another case of ganglioneuroma with metastases in lymph glands was described by Miller (1908) who saw well differentiated nerve cells and fibres in the secondary growths. In an excellent paper in 1909 Wegelin in describing a large retroperatoneal ganglioneuroma in a girl aged 20 was the first to demons trate differential staining of neurolibrits in the tumour cells and nerve fibres by the Bielschowsky method

Fail. (1907) was the first writer on ganglioneuromas to support the cell chain theory of the origin of nerve fibres. He believed that in a large retroperitioneal tumour which he examined he could trace the origin of the nerve fibres from the Sehwann cells independently of the ganglion cells a belief which his poor illustrations did little to support. The controversy between the neurone and cell chain theories was voiced in many subsequent reports of ganglioneuromas but since the final proof of the correctness of his s neurone theory by the experimental work of Harrison (1908) this controversy is now only of historical interest and mry be dismissed by referring to the discussions of it from the pathological aspect by Hertheimer (1914) and Wahl (1914)

In the subsequent development of our knowledge of the ganglioneuromas the following principal landmarks may be mentioned. Herkiemier's piper in 1914 was a most excellent account with a full discussion of all previous reports of ganglioneuromas neuroblistomas and chromaffin tumours and of the listo genetic kinship of the three types. Another comprehensive review in the same year was that of Wahl who also stressed the interrelationship of the three varieties of sympathetic neural tumours and who described in adrenal tumour containing all three kinds of tissue. Robertson (1915) emphasized the occurrence of tumours of transitional or mixed ganglioneuroblastoma structure presenting all possible combinations and degrees of differentiation. Dunin's paper in 1915 was an excellent and succincipaccount with admirable filtrations. Tumours of transitional and combined type and multiple tumours of the sympathetic system are the subject of another valuable recent paper by Wahl and Craig (1938). The tumour described by Cappell (1929) was a notable example of a large beingin ettiopertioneal

or idult life and in a few cases small quiescent ganglioneuromas have been discovered incidentially at necropsy in middle aged or old people, e.g. in Weichsel bium scase at 76 years of age. The approximate age distribution may be judged from the following figures. In Hervheimer's review of 25 cases of adrenal ganglioneuromas with ages at the time of operation or death recorded. 15 were under 20 years of age. 2 were between 20 and 30.4 between 30 and 40, and 4 older. In Wahl's review of ganglioneuromas of all sites. 29 out of 47 cases were under 30 years of age.



Fig. 419—Case I. A group of nerve cells in a ganglioneuroma of the thoracic sympathetic than (< 120)

The following ease exemplifies the accidental discovery of a benign quiescent ganglioneuroma

Case I—Routine radiographical examination of the chest of a woman aged 24 Prior to her joining the Services showed a well-defined rounded shadow in the left lung field thought to be a hydatid. After 2 years work in the Land Army without disability, she contemplated marriage and returned for advice. Skiagrars showed no change in the mass which was seen to be behind the lung. Operation by Mr. C. J. O. Brown disclosed an ovoid paravertebril tumour overlying the heads of the 5th to 7th ribs, this was 12 centimeters in main diameter and weighed 16 ounces. To the naked eye it resembled soft codematous fibrous tissue throughout. **Meroscopicull** it consisted of abundant non medullated nerve fibres accompanied by much fibrous sheath tissue and of scattered small groups of rounded 5s inputatives graphon cells (Fig. 419).

In view of the relative benignancy and slowness of growth of these tumours it is clear from the foregoing facts that they must take origin very early in life. It seems probable that their time of origin may be identical with that of the neuroblastomas, that the entire group of tumours is dysontogenetic or embryone in character, and that they differ amongst themselves only in rate of growth and hence mahgnancy. Rapidly growing tumours will make their clinical appear ance at an early age and will kill speedily, slowly growing well differentiated.

Ewing s syndrome. No doubt even when this is achieved there will still be a great preponderance of eases in infancy and early childhood, but this will certurily be less extreme than is at present supposed.

Landau and others have emphasized the general correlation between the age of apperrance of the tumours and their degree of histological differentiation and clinical malignancy. The earliest appearing tumours are usually the least differentiated most rapidly growing and most speeduly fatal. Thus tumours producing the Pepper syndrome present at birth or appearing during infancy are usually very rapidly fatal and consist wholly of diffuse round celled growth in which rosette formation is often indistinct or absent. Tumours producing Hutchison's syndrome appear on an average a little later often in children between 2 and 8

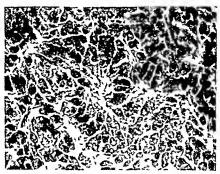


Fig. 418 -Detail of neuroblastic rosettes from the same tumour as Fig. 417 (x 500)

years old are a little less rapidly fatal and consist of tissue which though cellular and rapidly growing frequently shows rosettes and which is sometimes associated with well differentiated gangloneuromatous tissue in the primary growth (e.g. Cases III and IV below). Neuroblastomas in older children adolescents and adults are often of slower growth (e.g. 4 years. known duration in Case VII below) and may show a high degree of rosette and fibril differentiation. It must be admitted however that there are many exceptions to the general rule of parallelism between the age of onset and the degree of malignancy of the tumours (re. Blacklock).

(2) Canglioneuromas

As might be expected from their greater differentiation and slower rates of growth ganghoneuromas make their presence known rather later on the average than neuroblastomas. While many of them appear during childhood in a considerable proportion of cases their appearance is delayed until adolescence

must be treated with caution, in Blacklock's series the reverse was the case I know of no reported case of bilateral adrenal ganglioneuroma

(2) Multiple primary tumours

While metastasis certainly accounts for some of the bilateral adrenal growths, there is no doubt that primary affection of both adrenals occurs. Thus, Landau observed neuroblastomatous replacement of the medulia of both glands in a new born infant in which the liver was the only other viscus affected. Wright described bilateral adrenal tumours in a still born child, and in Potter and Parrish's case (also recorded by Wells), an 8 months foetus exhibited not only large bilateral tumours involving both adrenals but also widespread neuro blastomatous and ganglion cell tumours of sympathetic ganglia, the vagus nerve, and the wall of the bladder Pick indeed thought it possible that, since sympathetic cells are widely distributed in the body, multicentric origin might account for secondary growths in other situations, such as the liver and skull, but it is clear that genuine metastasis is responsible for most of the secondary tumours in viscera and bones. Genuinely multiple primary tumours in different parts of the sympathetic system are certainly rare, a typical example is reported by Wahl and Craig who also give other references. Rare cases like those of Knauss, Beneke and Kredel, and Smith, with many subcutaneous ganglioneuromas presumably arising from the perivascular sympathetic nerves, constitute a special Smith's case is particularly notable in that the subcutaneous tumours had been present since birth, and necropsy disclosed also an adrenal neuro hlastoma

(3) Neuroblastomas and ganglioneuromas of abdominal viscera

Other than the adrenals and mam sympathetic nerves, tumours have been observed in the uterus (Pick., Fingerland and Śikl.) mesentery (Jones), intestine (Poate and Inglis), and bladder (Potter and Parrish). Ritter's report of 2 cases of 'neuroblastoma of the intestine' in elderly people is unconvincing, the microphotographs of his first case indeed strongly suggest an argentaffin carcinoma.

(4) Neuroblastomas and ganglioneuromas of the central nervous system

It is very doubtful whether neuroblastomas or ganglioneuromas ever occur in the central nervous system. As to the former, many workers have looked upon the medulloblastomas as "neurocytomas" or as ambivalent growths representing both neuroblasts and spongioblasts. While this may indeed be the case, the nature of the medulloblastomas is still unsettled (see discussion by Cox, 1933, and also in Chapter 52), and there is certainly no warrant for grouping them and the retinal tumours along with the adrenal and sympathetic neuroblastomas, as Ewing has done. Such an artificial identification of three quite distinct kinds of tumours, merely because they are all malignant, poorly differentiated cellular neural growths occurring early in life, is to be strongly deprecated

The diagnosis of 'ganglioneuroma' which has been made for occasional tumours of the brain or cord must also be questioned. The first report of this kind was that of Worcester (1901), followed by those of Schminke (1910)

tumours will often have a deferred entrance on the clinical stage and will be less rapidly dangerous or may even remain quite harmless into old age. We will return to this subject later in discussing histogenesis

SEX INCIDENCE

The sexes differ little, if at all, in their proneness to ganglioneuromas and neuroblastomas. Some series of eases and reviews have suggested a slightly greater incidence in females than in males, e.g. in Herxheimer s review of adrenal tumours, there were 17 female eases of ganglioneuroma to 6 male and 13 female eases of neuroblastoma to 7 male 25 of 40 eases of ganglioneuroma reviewed by Wahl were in females, Scott and Palmer's review of extra adrenal neuro blastomas eomprised 18 female and 9 male eases and 11 of Blacklock's 18 cases were in female children. However, these numbers are all small and the sex differences not very great and a review by Scott and co-workers of cases of adrenal neural tumours covered 64 males and 53 females. Further collected figures will be necessary to determine whether any real difference of sex incidence exists.

SITES OF ORIGIN

(1) Adrenal glands and sympathetic ganglia

Almost all neuroblastomas and ganglioneuromas demonstrably arise from the adrenal clands or sympathetic nervous system. The adrenal glands are the most frequent single site of origin of these tumours accounting for about one third of all cases The abdominal and pelvie sympathetic chains and associated main ganglia the coeliae and mesenteric ganglia are the sites of origin of about another third of the tumours while the remaining third arises from the cervical and thoracie parts of the sympathetic chains or from small peripheral ganglia situated in the viscera themselves Thus the adrenal glands and abdominal parts of the sympathetic system are the sources of two thirds or more of the tumours and most of these probably about one half of all tumours arise in the adrenal glands of the great ganglia in their immediate neighbourhood. Avail able records suggest that ganghoneuromas are somewhat less frequently of adrenal origin than neuroblastomas. Useful reviews of the distribution of the tumours are those of Wahl Wahl and Craig Scott and Palmer and McFarland and Supplington Reports and reviews of cervical tumours include those of McFarland and Sappington Land and Shumaeker and Lawrence

The right and left sides uppear to be about equilly affected contrary to the impression obtained by some of the carrier workers from review of the few cases first recorded. Thus in 1909, Wegchin found 14 of 18 recorded sympathetic and adrenal ganglioneuromas to be left sided a difference which he suggested might be related in some way to the asymmetry of the embryo. However larger series of exists show that the difference which impressed Wegclin was fortuitous. Thus of 116 adrenal neuroblastomas reviewed by Scott et al. 47 were right sided of 53 left sided and 16 bilateral. The figures given by Scott et al suggesting that right sided adrenal neuroblastomas occur at earlier ages than left-sided ones

a stroma to the neuroblastic or ganghoneuromatous growth, and hence that strictly speaking there are no such turnours as ghomas. Singer and Sciler's descriptions and generally poor photographs will not convince many to their belief, which is mentioned here only as an example of the surprising extremes to which histo pathologists can be led by a pet hypothesis and a collection of stains.

COEXISTING DEVELOPMENTAL ABNORMALITIES

Since neuroblastomas and ganglioneuromas take origin duting the foetal or early post-natal period, it is pertinent to inquire whether they show any association with other disturbances of development. Such association has I believe, been observed in only 3 cases, in that of Mittelbach and Szekely and in 2 cases mentioned by Wells. In the first case a male infant exhibited, in addition to a left adrenal neuroblastoma with hepatic metastases, bilateral cleft lip and plater, microcephaly, defective corpus callosum, and patent ductus arteriosus. One of Wells is cases was that of a fulf-term female foctus with a tiny neuroblastomatous focus in one adrenal, and also hydrocephalus, extensive spina bifida, coarctation of the aorta, patency of the ductus arteriosus, absence of the left ureter, and a malformed rib. In a second case, Wells saw in a slightly premature male foctus, a small neuroblastoma of the right adrenal, and also persistent vitelline duct, vascular anomalies of the brain, and a thymic eyest.

HISTOLOGY

Here it must be recalled that neuroblastomas and ganglioneuromas are not distinct species and that tumours of mitermediate and mixed structure frequently occur. We will consider the structure of each of the three varieties in turn

(1) Neuroblastomas

The most rapidly growing of these tumours, e.g. many of those responsible for the Pepper syndrome and some of those responsible for the Hutchison syndrome, show little or no sign of recognizable neuroblast differentiation, they consist of closely aggregated small rounded or polyhedral cells devoid of arrangement except in so far as this may be determined by the pattern of the tissues infiltrated. The diffusely cellular undifferentiated character of these growths accounts for their having been classed by their first discoverers as "round celled sarcomas". The cells are fairly uniform in size and appearance, being usually 8 to 12 microns in diameter, with scanty ill defined cytoplasm, and each with a single spherical or slightly ovoid nucleus 5 to 8 microns in diameter. Mitotic figures are plentiful.

Less rapidly growing neuroblastomas show various stages in the early differentiation of neuroblasts, namely, grouping of the cells in rosette like clusters and the development of cell processes and young nerve fibres. These fibres constitute the centres of the rosettes or form parallel bundles. In section, each rosette consists of a group of 20 or 30 cells arranged in a ring between 30 and 80 microns in diameter around a central nucleus free fibre zone devoid of a lumen. These rosettes exactly resemble those of developing sympathetic ganglia (compare Fig. 416 with Figs. 417, 419, 423 and 429). The cells forming a well differentiated

Robertson (1915) and others More recent reviews and additional reports include those of Watjen (1930), Courville (1930 and 1931), Alpers and Grant (1931), Cox (1932) Kernohan et al (1932) and Singer and Seiler (1933) The only one of these tumours which I have personally studied is that of Cox whose paper and figures. I think it correct to say, appear to substantiate his diagnosis of ganglioneuroma" more convincingly than those of any other contributor in this field and with whose diagnosis I at that time agreed Yet Cox himself, in the light of further experience, is now fully satisfied that his former diagnosis was incorrect and that his tumour was an astrocytic glioma the cells of which somewhat resembled nerve cells in their structure and staining properties. I have his permission to record his changed opinion which from my own re-examination of his specimen, I share The following quotation from a later paper by Cox (1933) epitomizes well our reasons for revising our opinion regarding this particular specimen and for rejecting as unproved the diagnosis of 'ganglio neuroma' by the other writers ented above. Speaking of tumours so named Cox says. It is probably better at present to preserve an open mind concerning the true nature of many of these tumours Tumour astrocytes may be exceedingly bewildering not only in their general shape but in the appearance of the nucleus

Cells showing a nucleus with a large central nucleolus must not be considered as neuroblastic unless there is undoubted evidence of the presence of neurofibrils and Nissl's bodies. Many of the large protoplasmic tumour astrocytes may also be impregnated with certain of the silver stains, and if the cytoplasm contain granular degeneration products they may suggest by their appearance the presence of Nissl bodies. Cox also stresses the frequent inclusion of non neoplastic cells both nerve cells and gliad cells, in the tissues of brain tumours—a further possible source of error in the identification of growths of uncertain nature.

For the foregoing reasons, I find all the reports which I have read of ' ganglio neuromas ' of the central nervous system unconvincing I believe that most of these tumours were gliomas usually large celled astrocytomas in which resem blance of some of the cells to nerve cells in appearance and staining properties has been wrongly construed as identity, or in which included nerve cells have been mistaken for tumour cells Too much reliance has been placed on supposedly ' specifie ' stains, silver impregnation methods in particular are very fielde especially when applied to the highly variable tissues of tumours and to necropsy The haphazard use of one specife' method applied to only a few sections of a tumour has too often been the practice. He who believes he has a specimen of ganglioneuroma of the brain must competently apply a variety of staining methods with appropriate controls, he must very critically evaluate his results, and he must pre ent photographic evidence of the validity of his conclusions as clear and unmistakable as that afforded by specimens of sympathetic ganglioneuromas like those of Dunn Cappell and others Nothing short of such complete demonstration can prove the existence of a central ganglio neuroma The nerve-cell-containing growth of the third ventricle reported by Le Marquand and Russell v as a hamartoma and not a true tumour

It is relevant to refer here to the arresting view of Singer and Seiler (1933) that the essential tumour parenchyma of all gliomas consists of immature or mature nerve-cell tissue that all neuroglad elements in brain tumours are merely

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sympathetic ganglia and may be surrounded by satellite or mantle cells (Cannell) The cells commonly occur in large or small groups interspersed amongst the bundles of fibres

(b) The nerve fibres (Figs 419, 422, 425, 427)

These occur in irregular tangles or more often in interlacing well defined bundles measuring up to 0.5 millimetre or more in width. Some bundles consist of fibres only, unaccompanied by neurolemmal cells. Others contain plentiful Schwann cells, and their structure closely resembles that of normal non meduliated nerves (Fig. 427) Medullated fibres are abundant in only a minority of tumours The nerve fibres can be stained specifically by the Bielschowsky, Ranson, Bodian or Caral methods (Fig. 422) The fibres may appear to be excessive in comparison with the number of nerve cells in the tumour (Cappell)

(c) Connective tissue stroma

This varies in amount. It is often scanty, consisting only of blood vessels with their perivascular tissue penetrating the growth and of fine collagenous strands accompanying bundles of nerve fibres Less commonly, as in Cappell's tumour, it is more abundant and may become oedematous. The fibrous fasciculated appearance of ganglioneuromas on section is due more to their bundles of nerve fibres than to their connective tissue content Collections of leucocytes may be present, especially in degenerated areas. In one of my specimens, plasma cells were plentiful in nerve fibre areas

(d) Deceneration

Degenerative changes are common enough in the more malignant tumours of this group, but are not usually prominent in well differentiated ganglioneuromas It affects chiefly single cells or small groups of cells and leads to a fine granular, rarely massive, calcification Specific stains may reveal signs of degeneration in some of the nerve fibres in the form of varicosities or end bulbs Fluid cysts occasionally develop in ganglioneuromatous tissue, as in Jones's case

(3) Tumours of transitional or mixed structure ('ganglioneuroblastomas')

Many of the tumours called ganglioneuromas should teally be included in this group, since they show varying degrees of obvious immaturity and proliferative activity of some of their cells Beneke (1901) was the first to recognize this transitional character, which was later emphasized by Wahl Robertson, Dunn McFarland and Sappington and Wahl and Craig The following possibilities are realized in different specimens of these growths (i) Parts or the whole of a tumour may show transitional or meompletely differentiated structure, abounding in cells intermediate between neuroblasts and ganglion cells. All degrees of differ entiation may be seen in one tumour, ranging from rosettes to fully formed nerve cells and fibres (ii) A tumour predominantly neuroblastomatous may show differentiation of young nerve cells in places (see Bulbring, Capon, and Fig. 417) Cushing and Wolbach recorded a tumour which initially neuroblastomatous, attained increased differentiation later (iii) A predominantly ganglioneuromatous tumour may contain more or less immature neuroblastomatous tissue, and the latter may outgrow and invade the former, metastases are of neuroblastomatous

rosette are often pear shaped with their stalks directed centrally to become the young nerve fibres of the centre of the rosett. Increasing differentiation renders this fibrillar structure more distinct and produces also strands of parallel fibres which now stain specifically as nerve fibres. Still further differentiation makes the cells more like nerve cells and the tumour now occupies a borderline position between neuroblastoma and gangloneuroma. All these changes have their counterparts in the differentiation of normal foetal sympathetic ganglia. Stromal connective tissue is scanty in neuroblastomas and no distinct Schwann cells occur in them.

As with other classes of tumours, different parts of a neuroblastoma may show different degrees of differentiation. A tumour, the bulk of which is diffusely cellular and unidentifiable from its structure, may show distinct rosettes in one region only. Usually this is in the primary growth but sometimes a metastasis may show it distinctly as in the following case.

Case II (Willix 1934 No 297)—A girl aged 13 years had suffered from abdominat enlargement and cachevia for 9 months before her death Accepts showed a huge left adrenal tumour invading surrounding organs and discrete metastases in liver lungs and ribs Histology—The bulk of the growths showed a diffuse round-celled structure but rosette formation was visible rather indistinctly in parts of the adrenal tumour and much more distinctly in some of the hepatic metastases

(2) Ganglioneuromas

The degree of cellular differentiation in ganglioneuromas varies Many of the timours so designated contain plentful immature proliferating cells and belong strictly speaking in the group of intermediate timours discussed below

In pure fully differentiated being ganglioneuromas like those of Loretz, Weichselbnum Wegelin Stewart and Cuppell the cells closely resemble normal nerve cells and there are plentiful bundles of normal looking non medullated fibres accompanied by Schwann cells. In the more common less completely differentiated tumours many of the cells though unmistakably nerve cells show various abnormal or immature forms and the fibres are less perfectly organized into bundles and less regularly accompanied by neurolemmal cells. Let us consider in turn the nerve cells the nerve fibres the connective tissue stroma and degenerative changes observed in ganglioneuromas.

(a) The nerve cells (Figs 419-421 425 and 426)

These range from 15 to 100 microns or more in main diameter they are ovoid pyriform pyrimidal or irregular in shape and have one two or more processes. Nuclei measure up to 20 microns or more in diameter they are most frequently single but cells with multiple nuclei even 10 or 12 or more are common. Each nucleius usually has a single prominent nucleolus. Mitotic figures which may be plentiful in the small immature cells of retively growing ginglioneuroms are not seen in large well differentiated cells. The cytoplasm may appear dense and nearly homogeneous or finely or coarsely granular Appropriate strins may sometimes display typical Nissl's granules and intra cellular neurofibrils (see Cappell's beautiful photographs). Quite commonly brown pigment is visible in the cytoplasm of some of the cells. In highly differentiated rumours, the ginglion cells may closely resemble those of normal

between neuroblastoma and ganglioneuroma. Most of the neuroblastomatous tissue was diffusely cellular and devoid of rosettes but in some places large well developed rosettes with plentiful central fibers were present. The areas of intermediate structure consisted of pleomorphic cells 15 to 20 microns in diameter some of which showed multiple nuclei and others mitotic figures. All transitions could be traced between these and the less differentiated neuroblastomatous cells but in the sections studied no transitions to the fully differentiated ganglioneuromatous tissue were seen. It was clear that the latter had suffered invasion by the more cellular active growth which penetrated into bundles of nerve fibres and into the bodies of livre, eaplique cells and in these

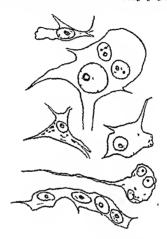


Fig. 421—Case III Driwings of individual cells from same section as Fig. 420 showing characters of nuclei and Nessla granules in some cells. (x 600)

areas iron haematovylin staining revealed varicose degeneration of fibres and the for mation of end bulbs. The metastatic growths consisted mainly of diffuse neuroblasto matious issue with occasional imperfect rosettes. but in some of them especially in the pulmonary and skull metastases; there were areas of transitional structure with pleomorphic cells. No well formed ganglion cells were found in the metastases.

Case IV—A boy aged 2 years was admitted to hospital with a brief history of paress which legs and swelling of the evelus. Examination showed multiple soft swellings on the skull which led later to propiosis of the right eye. Skagrams showed erosions of the outer table of the calvarium and also patchy rarefaction and periosted inside the management of the shafts of the bones of both legs and both humer; giving appearances which the radiologist stated were identical with those of Ewing's tumours. Accrops (by Dr. John Fulton of Launceston Taymania) 3 months later showed in the right adrenal gland a firm white well defined ovoid tumour 2.3 centimetres in main dameter clothed by a thin layer of adrenal contex. The left adrenal was normal. The retto peritioneal lymph glands were enlarged by soft white growth and a mass of sundar growth.

type, though they may show some degree of nerve cell differentiation (Compare the cases of Beneke Miller Berner, Jones, Dunn Wollstein and Heinriei) The following 3 cases illustrate these and other features in the structure and behaviour of these tumours

Care III—A boy aged 4 was admitted to hospital because of pain in the hip and refusal to use the limb Examination showed no abnormality of the hip but there was a palpable left upper abdominal mass. Operation disclosed a large inoperable retro peritoneal growth surmounting and involving the left kidney. X ray freatment gave no rehef and the child died 3 months later. Necropsy showed a large fobulated growth 15 centimetres in diameter enveloping and invading the upper pole of the kidney and tail of the panceras infiltrating the posos muscle and fusing with tumour deposits in



Fig. 420—Case III Well differentiated part of retropersioneal ganglioneuroma (Nissis stain) (\times 85)

neighbouring lymph glands. The left adrenal gland was firmly fused to the growth but intact. On section parts of the periphery of the growth consisted of firm fibrous fasciculated tissue with a smooth encapsulated surface while the remainder consisted of soft white growth with areas of yellow degeneration. Many of the abdominal lymph glands were enlarged by soft growth and there were multiple discrete metastases in the lungs liver right kidney right adrenal skull vertebrae and ribs. In the skull the tumours formed large bosses affecting both the calvarium and the base showed fusiform swellings in which the shafts of the bones were intact but soft growth replaced the marrow and expanded the periosteum away from the bone of new formed bone projected from the bone surfaces into the subperiosteal masses of growth. Histolize (Figs 420-423)-The fibrous-looking areas of the primary tumour showed well differentiated ganglioneuroms with groups of large nerve cells and many well formed bundles of non medullated fibres accompanied by plentiful Schwann cells Some of the nerve cells gave characteristic tigroid staining by Nissl's method and the nerve fibres stained specifically by Cajal's silver pyridine method. Some of the nerve cells were multirucleated but no mitoses could be found in them. The soft parts of the growth consisted of neuroblastornatous tissue with some areas intermediate in structure

similar growths. Skiagrams of pieces of ribs and skull showed that the tumours were traversed by bony spines projecting vertically to the surfaces of the affected bones (Fig. 424.) Histology (Figs. 425-426.—The bulk of the right adrenal growth had the structure of a well differentiated ganglioneuroma with groups of large nerve cells and bundles of non-medullated fibres partly with and partly without accompanying neurolemmal cells. Some areas of the timour however consisted of tissue of varying degrees



Fig. 424 —Case IV Skiagram of piece of skull showing spines of new bone projecting vertically from both inner and outer tables (× 3)

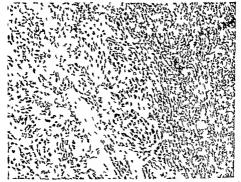


Fig. 425—Case IV Areas of imperfectly differentiated ganglioneuromatous cells and bundles of non medullated nerve fibres (x 70)

of immaturity including round-celled neuroblastic tissue with rosettes and pleomorphic celled tissue showing all stages of transition between the neuroblastic and ganglioneuromatous cells. All of the other growths consisted of immature cells of neuroblastication transitional type the latter forming extensive areas of pleomorphic cells often

5 centimetres in diameter occupied the paravertebral tissues around the body of the third lumbar vertebra. The liver contained many large soft tumours, and a single small nodule



Fig. 422—Case III Neuraxons in tumour selectively stained by Cajal's pyridine silver method (× 450)

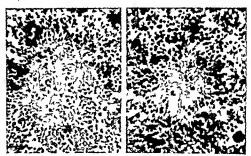


Fig. 423 – Case III. Rosettes with fibrils in neuroblastomatous part of tumour. (Iron haematoxylin stain.) (-300)

lay in the tail of the princreas. The ribs and skull showed many large growths, those in the calvarium forming smooth soft bosses projecting both ex emails and internally and confined by the pericranium and dura mater. The sphenoid and orbital bosses showed

as with so many other classes of neoplasms, all of the tumours constitute a single histogenic species, the individuals of which display a wide range of structure and behaviour. At one extreme lie the early appearing highly malignant, poorly differentiated "pure" neuroblastomas, at the other extreme lie the late appearing benign perfectly differentiated "pure" ganglioneuromas, in between the two extremes lie many tumours of "mixed" structure and of varying degrees of malignancy.

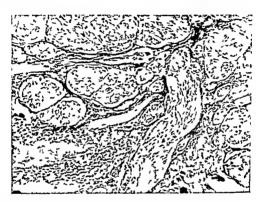


Fig. 427 - Case V Well differentiated nerve bundles with abundant Schwann cells (× 110)

HISTOGENESIS AND MODE OF GROWTH

From what has already been said it will be evident that our knowledge of the origin of the sympathetic neuroblastomas and ganghoneuromas is in certain respects clear and definite. These growths take origin from the undifferentiated proliferating neural tissue of developing sympathetic ganglia or the adrenal medulla, they are truly embryonic tumours, for they arise from immature formative tissue which has never attained complete adult differentiation. Most of them the neuroblastomas continue to consist of immature cells the proliferation of which goes on progressively at the embryonic or formative level and which never reach the differentiated quiescent state, while a few of them, the ganglioneuromas, grow more slowly and undergo, wholly or in part, differentiation into easily recognized nerve cells and fibres. In neuroblastomatous tissue, as in the foetal sympathetic ganglia the first recognizable stage in neurone differentiation is the appearance of rosette like clusters of cells around small central zones of fine nerve fibres and subsequent stages in the differentiation of the tumours resemble those seen in the normal development of the sympathetic system. In spite of the

multinucleated and with abundant initotic figures. None of the metastatic growths con tained any well formed ganglion cells

Care V—In April 1938 a male child aged 18 months was admitted to hospital because of abdomnal pain and constitution for several days. Examination revealed a large hard mass occupying the pelvis and lower abdomen and laparotomy disclosed a bulky well defined inoperable retropersioned tumour fixed to the anterior surface of the sacrum Microscopical examination of an excised piece of the tumour showed a mixture of ganglioneuromatous transitional and neuroblastomatous structure. Ganglioneuroma predominated but tissue of all degrees of immaturity was mingled with it including young pleomorphous nerve cells and small rounded neuroblasts with rocsette formation.

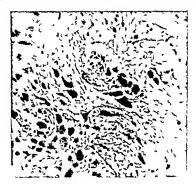


Fig 426 -- Case IV Detail of Fig 425 (x 230)

Bundles of well formed neive fibres with Schwain cells were plentful at the periphery of the tumour (Fig. 427). Progress—Deep X 79 treatment was given with benefit and in November 1938 the tumour was palyably smaller and fiarder and skiagrams showed some calcification in it. In April 1939 constitution again became troublesione and the mass had enlarged again and was compressing the rectum. Further X ray treatment was given with benefit and is August the tumour had become smaller and impolpable addominably though it could be easily left per rectum. In April 1940 it had again become palpable abdominably and rectally it was found that the pelva was atmost filled by a hard mass. Further X ray stradution was followed by some diminution of the mass which their remained but futtle afferred during the next 3 years. By May 1943 however there was some odefinis of the lower furths and the growth again nearly filled the pelvis

The three primary tumours just described are all malignant, and display a mixture of ganglioneuromatous and neuroblastomatous tissue. In Case III the latter has outgrown and is invading the former while in Cases IV and V the tumours show cells of all grades of differentiation and there is no evidence of invasive substitution of one component by another. From these and other reported cases it is clear that these growths are as much neuroblastomas as ganglioneuromas and that sharp distinction between the two types of growth is impossible. Here,

While it is probable that on the one hand an actively growing tumour may undergo retardation of growth and diminution or loss of malignancy, it is certain on the other hand that acceleration of growth with structural de differentiation and enhanced malignancy is a more common event, active neuroblastomatous growth overtaking and invading a relatively well differentiated ganglioneuro matous tumour (see Case III above)

METASTASIS OF NEURORLASTOMAS

Neuroblastomas, whether arising de noto or by de differentiation in pre existing ganglioneuromas, are highly malignant growths with powers of wide dissemination. In most eases the primary growth, usually in the adrenal or abdominal sympathetic system, is small and symptomless and the first or only symptoms are due to metastases in the liver or bones. So striking are some of these metastatic syndromes that they have been given coponyms. Thus Pepper's syndrome denotes great hepatic enlargement due to secondary deposits of neuroblastoma. Hutehison's syndrome denotes the presence of prominent skull metastases, and, as Colville and I first showed (1933), and as I confirmed in 1940 some eases at least of Ewing's syndrome are due to clinically obtrusive metastases of neuroblastoma in long bones. Neuroblastoma metastases may occur in almost any organ or tissue, but so frequent and so elinically important are hepatic and skeletal deposits, that we will consider these separately

(1) Metastases in the liver

True blood-borne metastases appear as multiple discrete rounded white or harmorrhagic growths, which may become very numerous, large and confluent Direct invasion of the liver, which occurs most frequently from right sided adrenal growths, should be distinguished from true metastases, though it may co exist with these. In either case enormous hepatic enlargement may result, e.g. in a case of Richards to 1,850 grammes in an infant 2 weeks old, in one of Blacklock's cases to 105 ounces (nearly 3,000 grammes) in a child aged 3½ years, and in Dunn's case to 7,290 grammes at the age of 14 Great hepatic enlargement is most often seen in young children or infants, not seldom being noticed at birth or soon afterwards (Pepper's syndrome) Microscopically the deposits in the liver are often more anaplastic than the parent growth and show less distinct rosette formation, but in some cases rosettes are well formed in the metastases (e.g.

(2) Metastases in boncs

These are very frequent, probably occurring in the great majority of fatal cases, though not always clinically obvious. They are also often much more widespread in the skeleton than might appear from clinical evidence or casual post mortem examination. Thus in cases with Hutchison's syndrome although main attention is naturally focused on the obtrusive skull tumours, careful radiography or dissection of the skeleton will almost always disclose less conspicuous involvement of many other bones, as in Webster's case and in Case IV above. So also the following cases both of which presented the syndrome of

truly embryonic dysontogenetic character of the tumours they are unlike the embryonic retinal tumours in showing no hereditary or familial tendency

There is general agreement that fully differentiated nerve cells are incapable of multiplication. If this is so then neuroblastomas and ganglioneuromas cannot arise from adult sympathetic or adrenal tissue. It is therefore pertinent to inquire at what foetal or post natal age proliferation and differentiation of formative sympathetic and adrenal neural tissue cease for this will determine the age limit for the possible origin of these tumours According to Wiesel (1902 and 1905) the formative cells, sympathogonia from which the adrenal medulia develops begin to invade the anlage of the cortex during the eighth embryonic week and subscouently collect centrally and this migration continues throughout foctal life and for some time after birth perhaps even until puberty. According to Poll (1905), the development of ganglion cells from sympathogonia continues until the tenth year. Theoretically then neuroblastic tumours could arise at any time prior to the tenth or twelfth year of life, though we might expect the majority to do so during the foetal or infantile period when cellular proliferation is most The age incidence of neuroblastomas and ganglioneuromas accords well with this expectation, as we have seen many neuroblastom's are known to be present at birth or soon afterwards and even the more slowly growing ganglioneuromas frequently make their appearance during childhood or adolescence

The incapacity of adult nerve cells for proliferation has an important bearing also on the mode of growth of established ganglioneuromas. As Wahl and others have pointed out and as I can confirm well differentiated nerve cells in these tumours do not participate in proliferative growth. Embryonic neuroblasts and immature nerve cells are the proliferating elements—and every growing tumour contains such cells in varying numbers and shows transitional forms between these and the fully developed ganghon cells. Strictly speaking then every ganglioneuroma still exhibiting any proliferative growth is really a transitional or mixed fumour as described above a ganglioneuroblastoma—and the only tumours fully entitled to be called being ganglioneuromas are those relatively rare completely quiescent tumours sometimes seen in adults, such as those described by Weichselbaum and Bruchanow, and my Case I.

A most interesting point discussed at some length by Wells is the possibility of an initially neuroblastomatous growth undergoing maturation and loss of malignancy with the prisage of time. Clerify all nerve-cell tumours must be neuroblastomas at their inception even those which later attain relatively benign ganehoneuromatous differentiation. Indefinite retention of vigorous neuroblastic proliferation is the mark of a miliginant neuroblastoma. The theoretical possibility that such a growth may later cease to probletate and may differentiate into a quiescent ganglion-cell tumour appears to have been realized in the case recorded by Cushing and Wolbach in which a paracetebral neuroblastoma in a child 2 years old retrogressed and exploratory operation 10 years later disclosed a small residual mass with the structure of an inactive ganglioneuroma. Wells cited other instances suggesting the possible cessation of growth and benign conversion of neuroblastomatous tumours and maturation of the tumour may have occurred also in Eden's Case 2. Needless to say careful follow up of such cases is essential before reaching final conclusions as to the sequence of events.

While it is probable that on the one hand an actively growing tumour may undergo retardation of growth and diminution or loss of malignancy, it is certain on the other hand that acceleration of growth with structural de differentiation and enhanced malignancy is a more common event, active neuroblastomatous growth overtaking and invading a relatively well differentiated ganghoneuro matous tumour (see Case III ahove)

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In their later stages metastatic neuroblastoma in bone may spread very widely and diffusely, often eventually involving a long bone for its entire length, producing patchy rarefaction of the medullary bone eroding the cortical surface and giving it a coarse sand paper texture and breaking through the expanded periosteal sheath to spread irregularly into surrounding soft tissues In spite of widespread involvement and patchy rarefaction the cortical layer of bone is seldom totally destroyed, and pathological fracture of long bones is unusual

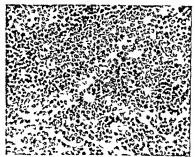
The route of dissemination of the skeletal metastases is clearly by the blood stream Section of various parts of the skeleton in eases with such metastases

massive Ewing's tumour of the femur illustrate well the widespread distribution of the skeletal deposits, as well as other features

Case VI (Reported in detail b) Cohille and Willis 1933 and see Figt 428, 429)—A gail 8 years old had a large fusiform tumour of the right fermu which had first been diagnosed as chronic osteomyelitis but which exploratory operation and biopsy showed to be a richly cellular round-celled non-osteogenic tumour. X say treatment gave prompt and striking improvement—and a confident diagnosis of "Ewing's sarroom was made



Fig. 428—Case VI Shingram (positive print) of femur showing onion skin layers of new bone cooked by metastatic neuroblastoma



Fir 429 -Case 11 Rosettes in priming adrenal neuroblastonia (240)

Accompt an months from the onset disclosed in addition to the large right femora growth smaller medulitry and subperiodical tumour deposits in the cranial bones mandible all veriebrae all ribs a erman right humanus, classicles pelos and left femor The right adrenal contained a small primary neuroblational with distinct rosettes Wilhighe discrete mediatalia, growths were present in the large limps both kidness left adrenal and reproperional lymph glands and microscopic deposits of tumour were also found in the solven.

neuroblastoma was made

Y ray therapy was applied to the fibular tumour and also to
the retropertioneal area
The tumour showed prompt dimmution but within four
months there was evidence of further disease in the lower half of the fibula and also in
the shaft of the femur and severe pelvic pain and oederna of the right leg later developed
Later still a large pelvic mass became palpable pathological fracture of the femur took
took place, and the girl died in a private hospital where no necropsy was obtained.

Although in this case necropsy proof of the primary source of the tumour was not available, the close clinical and radiographic similarity to my Cases VI and VII and to Aitken s case cited above, and the histology of the growth, leave little room for doubt as to its nature (For further discussion of "Ewing's sarcoma", see Chapter 43)

(3) Metastases in other tissues

(a) Lymph glands

Lymph glands are frequently affected, first those adjacent to the primary growth, and then more remote groups. Eventually lymphatic spread may become very extensive, so that a primary abdominal neuroblastoma may produce deposits not only in all retroperitoneal lymph glands but also in the pelvic, inguinal, mediastinal and cervical groups. However, clinically apparent enlargement of these seldom appears until a late stage of the disease. The affected glands are soft, white or haemorrhagie, sometimes discrete, sometimes diffusely fused Microscopically, rosettes can often be found in parts of the lymph nodal deposits.

(b) The lungs

The lungs develop metastases fairly frequently. The precise proportion of cases with dissemination by the blood stream in which metastases appear in the lungs is uncertain. In all 4 cases on which I personally performed necropsics (Cases II, III VI and VII above), multiple discrete pulmonary metastases were present. On the other hand, in many reported cases with Pepper's syndrome and in some of those with Hutchison's syndrome, no metastases have been observed in the lung. In Blacklock's 12 cases with complete necropsics, the only lung metastases seen were a few small subpleural nodules in 2 cases a paucity which Blacklock thought notable in view of the frequent presence of skeletid metastases. However, perhaps careful microscopic search might often disclose non proliferating tumour emboli arrested in the pulmonary arterioles, as in the well known observations of M B Schmidt on cases of abdominal careinoma.

(c) Other situations

Other situations in which discrete metastases have been observed include kidneys, adrenals spleen, pancreas, ovaries and subcutaneous tissues, most of which are represented in the cases recorded above. Cerebral metastases have not been reported. Peritoneal or pleural involvement has occurred frequently as a result of direct spread from growths in neighbouting organs or lymph glands, and pentoneal deposits in their turn may invade abdominal or pelvic viscera. Direct invasion of the pancreas kidney, spleen or vertebrae from primary adrenal or lumbar sympathetic tumours occurs frequently.

METASTASIS OF GANGLIONEUROMAS

"Malignant ganghoneuromas' with metastases in neighbouring lymph glands have been reported by Beneke Miller Berner and others From what has already

massive Ewing's tumour of the femur, illustrate well the widespread distribution of the skeletal deposits, as well as other features

Case VI (Reported in detail 5) Cohille and Billis 1933 and see Fige 428 429 —A grl 8 years old had a large fusiform tumour of the right femur which had first been diagnosed as chronic osteonychus but which exploratory operation and biopsy showed to be a richly cellular round-celled non-osteogenic tumour \ xay treatment gave prompt and striking improvement and a confident diagnosis of Ewing's sarroom was made



Fig. 428—Case VI Skiagram (positive print) of femur showing onion skin layers of new bone evoked by metastatic neuroblastoma



skin layers

Microscopically the skeletal growths often lack rosetles and fibrils and show only diffuse round-celled structure. Sometimes however, rosette formation is distinct and may afford strong biopsy evidence of the true character of a bone tumour of otherwise obscure nature, as in the following case.

Case IIII (D. B. P. II liman s case Lamection Teinnanta)—A girl 14 years old began rather suddenly to suffer from pain and swelling of her right fibula, thought at first to be due to subacute osteomyclitis. After 6 weeks radiographs (Fig. 430) showed a fundom soft incue mass around the upper half of the fibulal containing onton stin markings suggesting. I wing a tumour. At exploratory operation the expanded perioriteum was thickned and gritty on incising it, pale soft insue was found but no pus. A piece removed for microscopic examination showed a round-effeld growth with runny mi oses but also containing datinct rosettle with central fibril. Both the cells and rosettle were identical with those of other neuroblas omas examined, and a diagnosis of metastatic

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review and thorough study of an unusual case)

been said of the histology and mode of growth of these tumours it will be clear that their proliferation and metastasis must depend on the presence in them of immature neuroblastic cells. Fully differentiated ganglion cells do not multiply and hence a pure ganglioneuroma composed wholly of fully differentiated cells would be incapable of further growth or metastasis. The metastasizing elements of a tumour must be immature proliferating cells, which may or may not attain recognizable nerve cell differentiation in their new sites. As insisted on by McFarland and Sappington any growing nerve-cell tumour containing immature cells must possess some degree of actual or potential malignancy and powers of metastasis. We return, then to the view insisted on at the opening of the chapter neuroblastoma and ganglioneuroma are merely names applied to the poorly differentiated and the well differentiated members of a single class of growths within which all gradations of structure and behaviour are to be observed.

GANGLIONEUROMA AND NEUROBLASTOMA IN ANIMALS

Nieberle and Cohrs referred to a ganglioneuroma in a horse described by Gmelin they also stated that they had seen a similar tumour of the sympathetic chain with metastases in lungs and museles in an ox, but they gave no drails or figures. Curtis et al. recorded a ganglioneuroma of the optie nerve in a rat Ganglioneuromas are probably not very uncommon in fish. Haddow and Blake described a specimen and referred to two others.

In a 6-months old rabbit, Salaskin found a neuroblastoma of the neck with metastases in lungs liver and spleen instead of rosettes the tumour showed sinuous ranks of cells with fibril zones between them—"zebra markings In a 6-years old cow Baumgartner saw a tumour of the shoulder and presumed secondary growths in the lungs left kidney and abdominal lymph glands Mieroscopically these were said to show mingled neuroblastoma and ganglioneuromatous structure while this diagnosis may have been correct the figures do not convineingly establish it.

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CHAPTER 56

TUMOURS OF CHROMAFFIN TISSUES AND OF THE CAROTID AND AORTIC BODIES

MANY histologists and pathologists now doubt the correctness of the formerly prevalent view that the caroud and aortic bodies are paraganglionic or chromaffin tissues essentially similar to the adrenal medulia. On the contrary, evidence has accumulated (references by Bloom) that these bodies do not secrete adrenaline but are special chemo receptors concerned with the reaction of the blood Certainly, carould body tumours differ from the chromaffin tumours of the adrenal medulia in both structure and behaviour. Hence, while both kinds of tumours arise from tissues of neural derivation, they are best considered separately

CHROMAFFIN TUMOURS OF ADRENAL MEDULLA AND THE ORGANS OF ZUCKERKANDL

(1) Incidence, site and causation

Most chromaffin tumours—or phaeochromocytomas—have been found in joung or middle aged adults, and the two sexes appear to be about equally liable. In the majority of eases, the tumours are unilateral and solitary, but bilateral tumours are not rare (Schroder, Rosenthal and Willis, and other references by Edwards). Unequivocal instances of tumours of Zuckerkandl's bodies are very rare, in Cragg s case they were bilateral and associated with a carotid body tumour. The association of chromaffin tumours with neurofibromatosis, as in the cases of Suzuki, Kawashima, Herxheimer, and Rosenthal and Willis, is too frequent to be fortuitous. Staerumler's finding that chromic nicotine poisoning can engender adrenal chromaffin tumours in rats may afford a clue to causation, and further experiments are needed.

(2) Structure

To the naked e.e., the tumours appear as well circumscribed, but usually not encapsulated, spherical or ovoid masses of homogeneous grey or brownish tissue Most of them are less than 5 centimetres in diameter, but some are much larger, e.g. that recorded by Beit and Powell weighed 1,000 grammes. The smaller tumours are usually enveloped by a yellow layer of stretched adrenal cortex Fixatives containing potassium behromate or other chromium salts stain the tumours a dark rich brown, like that of the adrenal medulla itself.

Microscopically, the growths show a general resemblance to adrenal medullary tissue consisting of non compact groups of polygonal or irregular cells with intervening wascular channels. There is often much variation in size and shape of the cells, and multiple nuclei and vacuolation of the cytoplasm are both common Mitotic figures are usually scanty. Cell boundaries are often indefinite. Appropriate stain, susually reveal the presence of fat and lipoids. The intensity of the chromaffin Acaction varies from tumour to tumour and often from cell to cell of the one tumour. Sevki described apparently specific cosinophilic cytoplasmic

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874 TUMOURS OF CHROMAFFIN TISSUES, CAROTID AND AORTIC BODIES

reports of 143 cases, and in 1931 Rankin and Wellbrock a total of 196 Nearly three quarters of the tumours have been in patients between 30 and 60 years old, the mean age is about 42. But, as many of the tumours are known to be of very long duration—20, 30 35 years or longer—and as they are often of some size when first noticed the actual age of onset is probably in early adult life in most cases. Males and females are about equally affected. With rare exceptions, the growths are unilateral, but bilateral tumours are recorded by Lund, Rankin and Wellbrock, Chase and others. Chase saw carotid body tumours in two sisters the only record of familial occurrence. Cragg reported concurrent tumours of the left carotid body and of both organs of Zuckerkandl. Bloom saw two examples

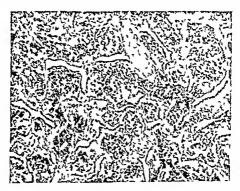


Fig. 431 —Carotid body tumour, showing groups of epithelium like cells separated by vascular spaces (× 120)

of tumours near the base of the heart in dogs, probably derived from the aortic bodies. I know of no instance of such a tumour in man

(2) Structure

The naked eye appearance is not inaptly described in the simile "potato tumour." The growths are smoothly lobulated, encapsulated, firm, homogeneous white or greyish they usually envelop the arteries at the bifurcation, or the vessels lie in deep grooves in the tumour. In size they vary from 2 to 6 centimetres or more in main diameter.

Microscopically, the tumours consist of masses of epithelioid cells resembling those of the carotid body, separated by vessels or strands of connective ussue (Figs 431, 432) The cells are usually large, polyhedral or irregular, with rather indefinite outlines, with abundant homogeneous or vacuolated cytoplasm in which fat droplets can often be demonstrated. The nuclei are usually single

granulation of formalin fixed tumour tissue and of normal medulla, this method deserves further study. Nerve bundles and nerve cells may be found within the growths, and Rosenthal and I observed chromaffin granules in these nerve cells as well as in the other tumour cells. Marginally there is often absence of clear demarcation between tumour tissue and neighbouring medulla, or the tumour cells imnigle with those of the surrounding cortex.

(3) Function

The functional activity of many of the tumours is not only suggested by their general resemblance to their parent tissue and the strong chromalin reaction of their cells, but is proved by their causing persistent or paroxysmal hypertension and other symptoms of hyper adrenalism, and by assays of tumour tissue for adrenaline. Belt and Powell Found an unusually large amount of adrenaline in their tumour—2 grammes per 100 grammes of tissue. Palmer and Castleman found. 2 milligrams of adrenaline per gramme of tumour. Vulpian's ferrice eliloride reaction and other staming and chemical tests for the presence of adrenaline have often been reported as positive (Edwards). There are now many reports of paroxysmal hypertension pallor flushing tachyeridia hyperglycauma and glycosuria, and other symptoms of sympathetic stimulation in patients with chromaffin tumours (Belt and Powell. Edwards. Palmer and Castleman) and in a few of these cases removal of the tumour has alleviated the symptoms.

(4) Malignant chromaffin tumours

In the great majority of cases chromaffin tumours are benign, growing slowly and neither invading surrounding parts nor metastasizing. King described a case in which there were bilateral adrenal growths and widespread metastases in other organs but although it is possible that king a diagnosis of 'malignant phaeochromocytoma may have been correct the smallness and bilaterality of the adrenal turnours raise at least the suspicion that they may have been metastases from some undetected primary growth and he gave no details of his technique in performing the chromaffin test. The malignant phacochromocytoma reported by Eisenberg and Wallerstein is very questionable there were large malignant growths in both the lungs and thyroid the adrenal tumours were bilateral and no details are given as to technique or results of the positive chromassin reaction which was said to be present. Such details are important in judging the merits of supposedly positive chromaffin tests this reaction is fickle and in tissues initially fixed in other solutions and not chromated until later it is capable of yielding both false negative and false positive results. None of the few malignant supposedly chromaffin-cell tumours reviewed by Belt and Powell were accompanied by symptoms of hyper adrenalism. Two supposed cases of malie nant paraganghoma with metastases reported by Lewis and Geschickter are unacceptable the reports are seanty and madequate

TUMOURS OF THE CAROTID AND AORTIC BODIES

(1) Incidence, site and causation

In 1905 Mönckeberg reviewed 9 previously reported examples of tumour of the carotid body and added 3 new ones. In 1929 Bevan and McCarthy collected

876 TUMOURS OF CHROMAFFIN TISSUES, CAROTID AND AORTIC BODIES

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sometimes multiple, mitotic figures are infrequent. The chromaffin reaction, which has often been said to be given by these growths and by the carotid body itself is faint and indefinite and not at all comparable with the intense reaction of the adrenal medulla, for example, Monekberg depieted it is only a faint diffuse yellow staining in some of the cells. Vulpian is test and other tests for adrenaline are negative, and adrenaline is not found in the tumours by assay it has often been stated that nerves are not present in carotid body tumours, but Chase found plentiful nerve fibres in his cases.

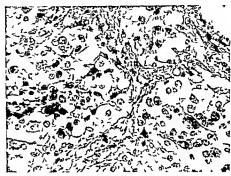


Fig. 432 -Detail of cells of the same tumour as Fig. 431 (x 450)

(3) Malignancy

With few and doubtful exceptions tumours of the carotid body are benign, growing slowly remaining sharply circumseribed and producing no metastase. Of some at least of the few recorded cases of supposed malignancy there is room for doubt regarding the identity of the tumours—these may really have been metastate deposits in the carotid lymph glands from undetected primary tumours elsewhere—The structure of benign carotid tumours is not highly distinctive, and if malignant tumours of this kind occur it is doubtful if they could be distinguished microscopically from metastate carenoma—Proof of the primary nature of a suspected tumour will depend on careful necropsy to exclude the possible presence of a primary growth elsewhere—As far as I know no reported case affords such proof

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CHAPTER 57

NEURO ECTODERMAL TUMOURS OF THE RETINA AND CILIARY BODY

TUMOURS arising from the neural tissues proper of the interior of the eye, ie those derived from the embryonic optic vesicle comprise the following

- (A) Retinoblastomas, arising from the still imperfectly differentiated optic part of the retina during foetal life or early childhood,
- (B) True gliomas (ostrocytomas), arising from the neuroglial cells of the fully developed retina,
- (C) Epitheliol tumours of the ciliary body or iris, and
- (D) Rare retinal tumours of other kinds

Group (A) comprises the great majority of retinal tumours, all of the others are very rare. It must also be noted here that acceptance of Dawson's view that the intra ocular melanomas arise directly or indirectly from the pigment layer of the retina would bring these tumours also within the scope of this chapter. This very distinct class of tumours however, is best considered along with their cutaneous counterparts in Chapter 58

An understanding of the origins of the retinal tumours requires a clear knowledge of the development of the retina from the optic vesicle a brief outline of which follows

DEVELOPMENT OF THE RETINA

Early in the fourth week of development of the human embryo the optic vesicles appear as hollow lateral outgrowths of that part of the primitive neural tube which later becomes the third ventriele. The stalk of the outgrowth is the rudiment of the optic nerve the vesicle enlarges and becomes invaginated to form the double layered optic cup (Figs 433-435). The outer layer of the cup retains its simple epithelial form and its cells become pigmented to form the pigment layer of the retina. The inner layer of the cup is the rudiment of the sensitive retina. At first this consists of a single layer of neuro epithelial cells but it rapidly thickens by proliferation of its cells the nuclei of which are studded densely throughout it except for a nucleus free zone on its inner or vitreous aspect The outer surface of the primitive retina is directed towards the pigmented epithelial layer but is at first separated from it by a slit which is all that remains of the eavity of the optic vesicle. Even after this slit is finally obliterated separation in this plane readily takes place as in detachment of the adult retina (Fig. 436). From the thickly nucleated embryonic retina all of the cellular components of the retina differentiate namely the outer stratum of sensory rod and cone cells the middle stratum of connecting or bipolar nerve cells the inner stratum of ganglion cells and nerve fibres and also the supporting cells of two kinds, the asteroid neuroglial cells or astromytes and the vertically arranged sustentacular cells or fibres of Mulier Cellular differentiation and stratification appear first

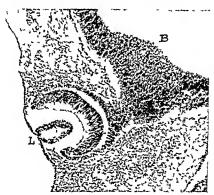


Fig. 433 —Section of 8 mm human embryo showing early optic cup in continuity with floor of brain B = brain L = lens (\times 90)

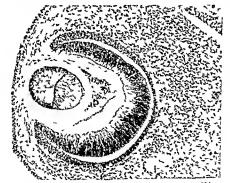


Fig. 434 -Section of optic cup of 12 5 mm human embryo (× 90)

at the centre of the optic cup and spread towards the periphery (Fig 435) and by the seventh focial month differentiation is nearly complete and the retina is sensitive to light. In the fovea and macular area, however, complete differentiation

CHAPTER 57

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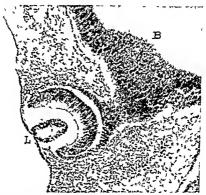


Fig. 433—Sution of 8 mm human embryo showing early optic cup in continuity with floor of brain B = brain L = lens (< 90)

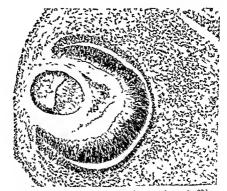
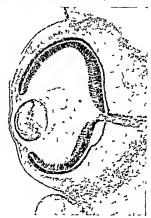


Fig 434 -Section of optic cup of 12 5 mm human embryo (× 90)

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is not attained until the fourth month after birth. The epithelium of the ciliary body and of the posterior surface of the ins represents the lip of the optic cup and the extreme periphery of the inner layer of the cup, and the insensitive ciliary part of the retina retains a primitive columnar or partly transitional kind of cotthelium which is demarcated from the sensitive retina by the ora serrata

It is relevant to note here the discovery of experimental embryologists that pieces of embryonic retina are capable of almost perfect self differentiation when isolated from their normal connexions and trinsplanted to other parts of the



I to 435—Section of optic cup and stalk of 28 mm human embryo showing early stratification of retina proper and dense pigmentation of outer layer of cup. (> 52.)

body (Lewis 1908) or cultivated in vitro (Strangeways and Fell 1926). This makes it less surprising that almost perfect differentiation of rosettes of rod and cone cells or even of stratified return like layers should be seen under the abnormal anatomical conditions prevailing in masses of tumour tissue.

RETINOBLASTOMAS

HISTORICAL OUTLINE

In their advanced stage of fungation on the face the retinal tumours of infancy and childhood are so distinctive and horrible that their recognition as a clinical entity long preceded their pathological study. In the latter half of the eighteenth century, they figured among the cases of fungus harmatods of the British

are recorded (Wells) In at least two thirds of the eases the tumours are discovered before the age of 3 years, and it is very rare indeed for them to be discovered after the age of 6. In Wintersteiner's large series, 314 of 467 cases (i.e. 67 per cent) were under the age of 3 when the disease was first recognized in 34 cases (7 per cent) it was known to be pre natal, and in only 10 cases did the disease appear after the minth year, the oldest patient being 16. In the Moor field's series of 163 cases, the oldest was 7 years of age. In a most exceptional case reported by Maghy, one eye was enucleated in the second year, failure of vision began in the remaining eye in the thirteenth year, and this eye was removed at the age of 20. An ocular tumour which first appears after childhood is almost certainly not a retinoblastoma.

(3) Sex incidence

Males and females are about equally affected, of the 759 cases of known sex reviewed by Berrisford, there were 398 males and 361 females

(4) Influence of the position in the family

Hemmes, Lange and others have given figures suggesting that first born children are the most prone to the disease. Thus Hemmes found that in 47 families each with an affected child this child was the first-born in 18 cases, while of 254 children other than the first born in these families, 29 were affected. It thus appeared that first born children were about thrice as liable to the development of retinoblastoma as those born later. It must be noted, however, that Hemme's cases were all sporadie ones with no evidence of a family tendency. Should such a series happen to include one or more families with many affected siblings it is clear that there would then be a much less striking difference between first born and later born children than in Hemme's series.

(5) Race meidence

In addition to reports of retinoblastoma affecting almost all European peoples the disease has also been seen in negroes (Cohen., Jaffe), Chinese (Hu. Ch'in), and other oriental peoples. Jungherr and Wolf give several references to retino blastomas in animals.

FAMILIAL AND HEREDITARY INCIDENCE

While many cases of retinoblastoma appear isolated or sporadic, no siblings or other relatives of the child being affected (Bernsford, and Hemmes) there are many striking instances of familial incidence and an inherited liability to the disease (Bell). Weller) One of the most remarkable of these was an Australian family recorded by Newton (1902), in this family 10 of 16 children died of retinal tumours, 7 having bilateral growths, and there was a history that the father's brother had died in infancy of an eye complaint. Another Australian family reported by Maher (1902) was notable not only because 3 of 4 children were affected, 2 with bilateral growths, but also because all 3 remained well several years after enucleation of their eyes.

The occurrence of retmoblastomas in members of two or more different generations of a family, indicative of a transmitted liability to the disease, is less

is not attained until the fourth month after birth. The epith-hum of the ciliary body and of the posterior surface of the iris represents the lip of the optic cup and the extreme periphery of the inner layer of the cup—and the insensitive ciliary part of the retina retains a primitive columnar or partly transitional kind of epithelium which is demarcated from the sensitive retina by the ora serrata

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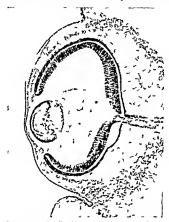


Fig. 435—Section of optic cup and stalk of 28 mm. human embryo showing early stratification of retina proper and dense pigmentation of outer layer of cup. (× 52)

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and orbital ussues were unaffected but both optic nerves were infiltrated and enlarged by growth as far back as the chasma (Fig 442). The brain showed over its entire surface a continuous layer of soft white growth up to 4 millimeters thick which also clothed the surface of the spinal cord. Marked internal hydrocephalus was present with moderate enlargement of the skull and exaggerated convolutional markings on its inner surface. In the diploe of the temporal and parietal bones some of the main vessels were accompanied by ramifying white strands of growth. No tumour deposits were found in any other bones nor in any cervical thorace or abdominal viscera. Microscopic examination showed the ocular tumours to be typical retinolastomas consisting maily of masses of rounded cells with plentiful areas of necross with some calcification but some areas of tumour showed well differentiated rosettes and fibrillated tissue (Figs 437 438). The tumour deposits in the optic nerves and on the surfaces of the brain and cord consisted of diffuse round celled growth devoid of rosettes and fibrils.

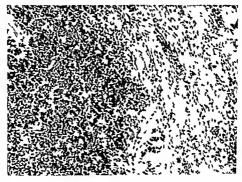


Fig. 437 - Case II Retinoblastoma showing areas of rosetted and fibrillar tumour (× 150)

As Duncan and Maynard point out in their report, the slightly different course of the growth in the twins was largely attributable to surgical interference in Twin I, in whom trephining of one eye was followed by extension to the orbit and massive cervical metastases, with earlier death and less pronounced intracramal extension than in Twin II Otherwise the 2 cases were strikingly alike in all respects

Case III was a female child born of the same parents 16 months after the death of the Gardner had one eye excessed on account of a large retinoblastoma which is depicted in Figs. 436–439 and 440. This tumour was better differentiated than those in the twins containing many beautiful rosettes however mixture figures were numerous. The retina was extensively detached but the growth was confined to the vitreal chamber and did not involve the optic nerve. Some months later examination disclosed a tumour in the other eye which however the parents refused to have removed. This grew steadily but was still confined to the eye when the patient was last seen at the age of 4 years.

commonly observed than its appearance in siblings. Weller has reviewed 30 recorded families in which such transmission occurred comprising 102 definite cases and 6 likely eases of the disease In 14 families the father of retinoblasto matous children had had his eye removed for this disease in his childhood in 7 families the mother had had retinoblastoma in childhood, and in 8 families the tendency was transmitted through non affected parents, in 4 instances through the father and in 4 through the mother brother or sisters or other relatives of the parents having had retinal tumours in childhood. Weller gives a record of a family in which retinoblastomas may have occurred in four successive generations though there is no proof of the nature of the disease in the two early generations proven retinoblastomas occurred in a father and his two daughters and the father's father and grandfather were both said to have had their eyes removed in childhood. A striking example of transmission from a grandparent to grand children through an unaffected mother is afforded by the family record given by Berrisford the grandfather had had his eye removed in infancy in 1859 and his son had had his eye removed for retinoblastoma in 1898 at the age of 3 years and had died when 15 years old the old man's daughter however escaped her brother's fate and remained unaffected but 4 of her 8 children developed retino blastoma bilaterally in 3 cases and all 4 died at or before their fourth year

The mode of transmission of the liability to retinoblastoma is unartain. There is no clear indication of either Mendelian dominance or recessiveness. There is no sex linkage and as the families cited above show transmission takes place about equally through either male or famile parents.

Although sporadic cases of retinoblastoma are more common than familial ones, from a genetic aspect the difference may be more apparent than real As Weller points out the first case to be observed in a family will necessarily appear to be sporadic, but if this individual survives he or she may later p opagate a retinoblastomatous family. Weller sums up the eugenic aspect of the subject as follows. Sterilization of any child who survives enucleation or irradiation for retinoblastoma and the interdiction of further progeny to the parents of a child with retinoblastoma appear to be justifiable measures.

Tisms with identical retinoblastomas have been recorded by Benedict (1929) and by Dunean and Maynard (1939). As I personally performed the necropsy and made the histological study of the tissues from one of the twins described by Dunean and Maynard and as a subsequent case of retinoblastoma occurred in the same family I give here a brief outline of the 3 cases which also illustrate other features of the decase.

Cases I and II were apparently identical famile twins of Italian parents. During the twin pregnancy the mother had had severe anasema from lead prosioning. At the age of 7 months both twins were found to have advanced bilateral retinal tumours. $T \sin I$ following a trephine opening of the right eye later showed extension of the growth into the right otheral tissues with subsequent orbital recurrence after enucleation of the eye as well as a large fungating mass in the right side of the neck. and death occurred at the age of 19 months. Necessity OP Montard) showed also extension along the optic nerve scattered discrete deposits of growth on the base of the brain and involvement of the right apical pleura doubtless from the large mass of secondary growth in the right side of the neck. No secondary growths were found in any other thorats, or addornial viscera. This II deed 5 months later at the age of 23 months. Necessary (HIII) showed extensive disorganization of the interior of both eyes by parth degenerated growths. The science

enucleation of both eyes without recurrence in either the orbits or cranial cavity, thus Collins (1896) reported 4 cases of bilateral retinoblastoma cured by enucleation of both eyes, and I have already cited a similar experience of Maher s

MICROSCOPIC STRUCTURE

In many retinoblastomas the bulk of the tissue consists of cellular round celled growth devoid of any special cellular arrangement, showing plentiful mutotic figures, and prone to patchy necrosis. In areas of necrosis, mantles of surviving tumour cells often persist around blood vessels, and some calcification of the degenerated tissues is frequent.

Parts of the growth, however, may show structural differentiation in the form of nestles or fibrillated areas or both Usually these are present in parts only of an otherwise diffusely cellular tumour, as in Case II above . but some tumours

show plentiful rosettes or fibrillation, as in Case III

The rosettes of retinoblastomas, which were first observed by Flexner and have never been described better than by him, are denicted in Fig. 439 Each rosette in section consists of a group of 15 to 40 or more clongated cells arranged radially around a central circular or oval cavity 10 to 60 microns or more in diameter. The nuclei of the cells occupy their outer or basal ends and he in a rather even ring at the periphery of the rosette. The apical or centrally directed parts of the cells tend to taper towards the lumen, some of them he in contact with each other, while some show fine sht like spaces between the tapering eells Near its apical end each cell bears a fine but distinct transverse mark where it traverses the delicate but distinct membrane which demarcates the lumen of the rosette The contents of this lumen may consist of distinct rod shaped or bulbous processes of the cells internal to the membrane, or of granular debris. As Flexner noticed, rosettes with distinct cell processes within the lumen contain little or no amorphous debris, and rosettes with plentiful debris show no distinct cell processes, and it is clear that the debris results from disintegration of the processes. The whole structure is unmistakably identical with that of the rod and cone layer and external limiting membrane of the normal retina, and even the contents of the lumen of the rosette resembles that of the sub retinal space of a detached retina in which rods and cones may still be distinct or may disintegrate to granular amorphous material (Compare Fig 436 and Fig 439)

The basal or nucleated ends of the rosette cells are crowded together and usually have indistinct outlines, but sometimes, as Flexner again noticed, a distinct fine fibrillary process may be seen to arise from the base of a cell and to penetrate amongst the surrounding tumour cells. The nuclei of the rosette cells are identical in appearance with those of the clustered unarranged tumour cells around. Each nucleus is spherical or ovoid, 7 to 10 microns in diameter and has a rather distinctive punctate chromatin pattern consisting or scattered fine particles accompanied by a few coarser particles, and no distinctly vesicular nucleolus. The unarranged tumour cells around and between the rosettes have scanty ill defined cytoplasm the nuclei often appearing to be naked. Mitotic figures occur in both the unarranged cells and in those of the rosettes. Occasionally, as Flexner observed, a rosette is seen with its lumen occupied by one or two round tumour cells, evidently intruders from the proliferating tumour tissue around

SITUATION MULTIPLE AND BILATERAL TUMOURS

Most of the tumours arise in the posterior parts of the retina, especially in its lower half. Even in early stages the ophthalmoscope often shows multiple foci of growth sometimes, a plentfull sprinkling of the whole retina with miliary growths. (Duke Elder) While some of these may be due to metastatic seeding that the vitrous or that the sub-retinal space behind a detached retina it is elear that many of them are multiple independent primary foci, as in Ch. in sease

Bilateral tumaurs are frequent, occurring in about 25 per cent of cases e.g. in 97 of 405 cases in Wintersteiner's series. Bilateral disease is much more frequent in familial and inherited cases than in sporadic ones, as is exemplified in Newton's Maher's and Berrisford's cases afteady cited and in Cases I II and III above

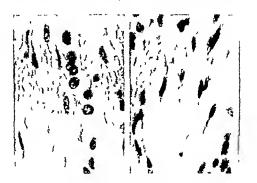


Fig. 438 -Case II Detail of fibrillar area of Fig. 437 (< 800)

The tumours may be discovered simultaneously or nearly simultaneously in both eyes and one or both growths may be present at birth. More often however there is an interval between the times of appearance of the timours in the two eyes. The interval is usually only a few weeks or months occasionally it extends to several years e.g. It years in Maghy scase. Bilateral growths are not due to spread from one eye to the other by may of the optic nerves but are independent primary growths. This is shown conclusively by the following facts. (a) Ophitial moscopic examination shows that the timours in the second eye arise in any part of the retina and do not necessarily or even usually appear at the optic disc. (b) The first affected eye has often been enucleated at an early stage when the growth is still purely intra-ocular and the optic nerve is microscopically free from growth. (c) When the second eye has been enucleated its nerve also has often been found unmodited. (d) Pattents with bilateral growths have survived

Fibrillated tissue is less common than rosettes, and indeed well marked fibrillary differentiation has seldom been mentioned at all in descriptions of the histology of retinoblastomas Case II (Figs 437, 438), however, affords a good example of a tumour with areas of prominently fibrillated tissue. The cells, many of which are elongated, are separated by masses of fine wavy fibrils more or less parallel in direction. The nuclei are similar in appearance to those of the more cellular areas of the tumour The cytoplasm is scanty and indistinct, but in places it can be clearly seen that the fibrils are processes of the cells fibrils stain rather faintly with the usual stains, and Van Gieson s. Mallory s and Masson's stains show that they are non collagenous. As my specimen was embedded in paraffin, it was unsuitable for applying special stains for neurofibrils or neuroglia, and I am not aware that this has ever been done convincingly with any tumour of this kind However, from the obviously similar nature of the cells of the fibrillated areas and those of the more usual round celled growth in other parts of the same tumour, and from the fact that the fibrils are processes of these cells, it seems clear that in this tumour at least the fibrils are of true neural. not neuroglial, character, and that they correspond to those of the plexiform or fibre layers of the normal retina

As long ago as 1904, Verhoeff observed that the supposedly round cells of retinal tumours are in fact often clongated, and in one tumour the cells resembled the bipolar cells of the adult retina, having a delicate process at each end. The processes were often quite long, stained only faintly and their ending, could not be made out. The tumor contained rosettes in great numbers. In at least three other tumors the writer has been able to make out numbers of cells with such processes. The cells described by Verhoeff were undoubtedly the same as those depicted in Fig. 438, and I am satisfied that his identification of them as bipolar cells of the inner nuclear layer was correct.

Growths with well developed retina-like structures, like that depicted by Susman, would afford the best material in which to display conclusively the nature and relationships of the fibrils

Do neuroglail cells and fibres ever differentiate in these tumours? There is no inherent improbability in such differentiation, but it has not been proved to occur. We have already noted Greeff's and Hertel's early claims to have demon strated neuroglial' spider cells' in retinal 'gliomas', and Leber's and Verhoeff's criticism of these claims. More recent workers who believe they have identified neuroglial elements in these tumours include Urra and Grinker, but their descriptions and illustrations are far from convincing. Neither of these writers displays any healthy doubts regarding the specificity of the silver impregnation method he has used, and neither gives any details of his technique, or any evidence that he has adequately controlled his results Grinker's claim to have identified astrocytes", "astroblasts", "spongioblasts" and "oligoden droglia' using an unspecified technique ("Kanzler" method according to one of the legends), will not satisfy many histopathologists, nor will Urra's highly diagrammatic drawings of all too-perfect 'astrocytes'. Neuroglial elements, both astrocytes and Muller's cells, may well occur as an accompanying stroma in the more highly differentiated retinoblastomas, just as Schwann cells occur in

Rarely a retinoblastoma shows retinal differentiation even greater than rosettes Elongated or irregular spaces may appear, into which project well

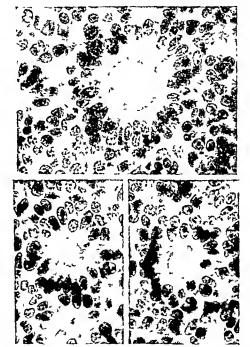


Fig. 439—Care III Retinoblastoma rosettes. Compare structure with that of Fig. 436. Note cells in mitosis in rosettes. (800)

differentiated rods and cones and which are surrounded by nucleated and fibrillary layers exactly reproducing those of the normal retina. Susman has depicted an instance of this rare type of growth, unfortunately without recording any details

is unwarranted, so are attempts to homologize the variants of retinoblastoma with the different types of cerebral tumours. The derivation of the retina from the primitive neural tube is no valid reason for applying to retinal tumours our notions of the histogenesis of cerebral tumours. The retina is not the brain, and the retinoblastomas are not like any of the tumours of the brain. No sub division of the retinoblastomas is necessary, these tumours form a single histogenetic group the origin and nature of which are perfectly clear. As in other groups of tumours, there is a considerable range of structure and behaviour within



Fig. 440—Case III Celloidin section of eye showing retinal detachment with retinoblastoma (×5)

the group, but this does not call for its sub division or for any elaboration of nomenclature

Mones of Spread and METASTASIS

(1) Intra-ocular extension

Forming first a nodule or plaque in the plane of the retina, a growing tumour may later project into the vitreous from the still attached retina, or more commonly

well differentiated ganglioneuromas but we still need proof of this by evidence much more substantial and precise than that so far advanced

HISTOGENESIS AND NOMENCLATURE

Comparison of the structure of the retinoblastomas and of the developing retinal leaves no room for doubt as to the correctiness of the view first advanced to Collins Ginsberg and Verhoeff and later crystallized in the name retinoblastoma, that these tumours are essentially embryonic, representing

immature developing retinal tissue. Those which continue to proliferate at the embryonic level fail to attain any structural differentiation, but when differentiation occurs it produces retina like structures most commonly rosettes of rod and cone cells less commonly fibrillary or plexiform retinal tissue and least commonly unmistakably retina like layers as in the case depicted by Susman. The identity of the constituents of a rosette with its typical elongated cells, its limiting membrane and its distinct rod like and cone like cell processes, cannot but be obvious to anyone who has examined a single good preparation of a retinoblastoma with well formed rosettes. Study of such a specimen will show how nonsensical is Fischer's suggestion that the embryonic tumours of the retina and the symnathetic system are essentially similar and should be classed together as neuroblastomas and Ewing's endorsement of this view in one place (on his p. 442) and his apparent rejection of it a few pages later (pp. 470-3) will seem pointless as well as inconsistent If Fischer, Ewing and others had read and pondered Flexner's excellent original description of retinoblastomatous rosettes and had carefully examined one good specimen of them they could not have written such absurdities

While Flexner and Wintersteiner correctly identified the rosettes as corresponding to the outer layers of the retina the implication in their writings and in those of others, that the rosettes represent superfluous foci of retinal cells (Cohnheim rests.) from which the rest of the tumour tissue grows cannot be accepted. The rosettes are not the original source of the tumour but merely foci of retinalised differentiation in the tumour tissue as it grows. The tissue of some retino-blastomas like that of some neuroblastomas matures to a greater or less degree as it grows. The tissue of some neuroblastomas produces ganglioneuromatous structure maturation of a retinoblastoma produces retinal the structure

While it is clear that all parts of the immature retina may be represented in the tumours it seems probable that the most frequent and main source of the growths is the outer nuclear layer. Not only do the rosettes represent outer nuclear layer cells with their attached rods and cones but some early tumours have been seen to be continuous with the outer nuclear layer and to have the still intact inner layers of the retina clothing them on their inner aspect (see Duke-Elder s Figs. 2.427 and 2.447). On the other hand some early tumours clearly arise from the inner nuclear layer as in Ch in s case. and of course fibrillated areas with bipolar tumour cells represent this layer. However the precise zone of origin of the tumours is probably immaterial multiplying embryonic retinal cells probably all have equivalent potencies for differentiation.

Sub-division of the retinoblastomas into several types with corresponding elaboration of nomenclature as proposed by Grinker Favaloro and Susman

the lamma cribrosa and directly into the substance of the optic nerve which is enlarged and partially destroyed by tumour (Fig. 442). Infiltration of the nerve may extend as far as the chasma. In some cases extension takes place cheftly in the sheath around the nerve, and the cerebral sub aractinoid space is speedly invaded. Once the tumour has reached the crainal cavity, either via the nerve itself or its sheath rapid extension in the sub aractinoid spaces of the brain and cord ensues. This may be either in the form of discrete scattered metastatic deposits by way of the cerebrospinal fluid as in my Case I, or in the form of a more or less continuous sheet of growth over the surface of the brain and cord as in Case II (depicted by Duncan and Maynard), and in the cases of Hu,

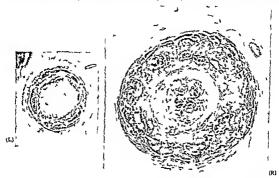


Fig. 442 —Case II Cross sections of optic nerves. The right nerve shows great distension of its sheath by growth and also a central mass of stowth, the sheath of the left nerve is less distended and the nerve isself nearly nated. (x 10)

Cairns and Russell, and others. The data mater and bones of the skull are not invaded from these intracranial growths, but there may be coexistent invasion of skull bones from the orbit, or intensity in them, or inconspicuous perivascular extensions into the diploe along the extra dural meningeal vessels, as in my Case II.

(11) Trans scleral extension to the orbit takes place principally along the pen vascular spaces of the vessels which perforate the sclera, the chiary attentes and the venae vorticosae. The growth fills the orbital cavity, may cause proptosis of the eye, and appears on the face as a horrible fungating mass which may attain an enormous size. From the orbit direct invasion of the bones of the skull often ensues. Invasion of the cranial cavity from these does not occur, though of course there may be coexistent intracranial extension wa the optic nerve.

(3) Metastasis

(i) Metastasis by lymphatic channels occurs only after extension of the growth to the orbit and face when metastatic growths may develop in the pre auricular the retina suffers detachment and much of the growth comes to he in the subretinal space (Fig 440). From the posterior half of the globe the tumour may spread forward to destroy the ciliary body and iris envelope the lens and invade the anterior chamber (Fig 441). Metastatic seeding may occur through either the sub-retinal space or the vitreous producing implants on other parts of the



Fig. 441—Eve of an infant with retinoblastomal showing spread of growth to citiary body and iris and over front of lens. (5)

retina choroid ciliary body or iris. Glaucoma degeneration and strophy of the intra-ocular tissues ensue.

(2) Fxtra-ocular extension

Extra-ocular extension of the growth takes place in two distinct ways (i) by the optic nerve and (ii) through the sclera to the orbital tissues

(i) Extension by the optic nerse is frequent and on its presence or absence post-operative prognosis largely depends. Most deaths from retinoblishming the due to intracranial extension by this route. The growth infiltrates through

however, is shown by Gifford's report of a case of retinoblastoma in a child of 3½ years, whose optic nerve after excision was found to be infiltrated right to its cut end, but who was well 20 years later, and by De Kleijn's report (cited by Gifford) of a similar case of a patient who remained well 6½ years after enucleation

The proportion of cures to be expected after enucleation is difficult to estimate with accuracy, but available figures (cited by Duke Elder) suggest that in operable cases, ie those with no clinically apparent extra ocular extension, more than 50 per cent can be cured by enucleation. The unfavourable results in the remainder depend almost entirely on infiltration of the optic nerves, micro scopical examination of which therefore permits fairly accurate prognosis in most cases. Reese found that in 52 per cent of 119 eyes enucleated for retinoblastoma the growth had extended through the lamina cribrosa into the nerve, and in 43 per cent extension in the nerve reached right to its cut end thus rendering the prognosis next to honeless.

Spontaneous retrogression of retinoblastoma is a rare but well authenticated event Duke-Elder cites 11 cases in which spontaneous cure has been recorded and the after-history followed for many years, and the subject is also discussed by Hine and by Wells In most of the cases, one eye has been removed because of a microscopically proven retinoblastoma, and then an ophthalmoscopically similar growth has appeared in the second eve and has retrogressed after attaining a certain size In some cases the eye containing the retrogressed tumour has been atrophicd and useless, in others a useful eye has remained The ophthal moscopic appearance of such a retrogressed tumour is distinctive (Duke Elder) In Knieper's case the right eye was removed at the age of 21 months and proved to contain a retinoblastoma, the left eye was also filled with growth, but the parents refused a second enucleation and the child was discharged. It was found 11 years later alive and well in an institute for the blind, with an atrophied lefteye In Stallard's case (cited by Duke Elder) retrogression followed a severe attack of scarlet fever, the patient subsequently had 2 children, both of whom had bilateral tumours In the cases reported by Hine, a father of 5 sons had had his left eye excised for retinoblastoma at the age of 2, and he also had a healed lesion in his right eye Of his 5 sons, one died when 6 months old the other 4 all developed retinal tumours, bilateral in 3 cases, and one of the children with bilateral tumours showed spontaneous retrogression of both of the growths It need scarcely be said that spontaneous cure by total degeneration of a retino blastoma is so infrequent that it cannot be seriously considered in assessing prognosis

TRUE GLIOMAS (ASTROCYTOMAS) OF THE RETINA

True astrocytic gliomas of the retina, comparable with the astrocytomas of the brain are very rare. Examples have been reported by Dejean (1934), McLean (1937), and Marks, Willis and Anderson (1939). My study of the tumour in the last cited case that of a girl of 11 years who was known to have had a slowly enlarging nodule near the optic disc since the age of 6 showed the tumour to be a smoothly hemispherical mass 9 millimetres in maximal diameter, Jying to one side of the optic disc replacing the external layers of the retina and clothed on its inner surface by the intact nerve cell layer of the retina. It consisted of a

and cervical lymph glands as in Case II From these the tumour may spread to the mediastinal and other lymph glands and blood-borne metastases elsewhere in the body may also be accompanied by deposits in the corresponding lymph glands

(ii) Metastasis by the blood stream is infrequent many cases succumbing to the local disease or its intracrantal extensions without showing remote dissemination. Blood borne metastases most frequently affect bones these metastases may be very numerous and widespread insolving both the medullary and subperiosteat tissues (Roman, Hu. Ch. in). Metastases in thoracie and abdominal viscera are rare in Wintersteiner's large series of cases the liver contained growths in only 7 cases the kidneys in 2, ovaries 2 lungs 1 and splen 1. Hepatic metastases were present also in Roman is Jaffe's and Ch. in a case subjudication in Lauber's case and ovarian metastases in Jaffe's case had deposits in the panereas and the muscles of the thigh. Lawson mentioned a deposit in the deloid muscle. The rarity of deposits in the lungs is particularly noteworthy.

The structure of metastatic growths as of all extra ocular extensions, is usually diffusely cellular and devoid of any recognizable arrangement or differentiation of the cells. Occasionally however, rosette formation may be observed as in a metastasis in the fibula in Roman's case.

Prognosis

Post-operative prognosis depends largely on the condition of the optic nerve of the excised eye. This should always be examined microscopically if it is infiltrated by growth the outlook is bad particularly if the infiltration extends to the divided end of the nerve if it is unaffected and orbital extension has not occurred the risk of recurrence is not great, and prognosis will now depend largely on whether a new tumour develops in the remaining eye. As we have already seen such bilateral development is most to be feared in cases vith a strong familial predisposition to retinoblasioma. Needless to say however regular and frequent ophthalmoscopie inspection of the remaining eye should be made in all cases over a follow up period of at least 2 or 3 years and should a new growth appear in this eye its prompt enucleation should be advised. If microscopic examination shows the nerve of the enucleated second eve also to be free from growth, then the p ognosis remains quite favourable. We have already mentioned cases of survival following bilateral removal of the eyes such as those of Maher and Collins and there is little doubt that lives have been lost as a result of temporizing on the part of the surgeon or unwillingness on the part of parents to consent to removal of both eyes. The proposition that death is preferable to permanent blindness from infancy of course does not be within the scope of pathological discu s on

The all importance for prognosis of the condition of the optic nerve of a retinoblasionatious eye has a bearing also on surgical technique clearly in removing such an eve as much as possible of the optic nerve should be removed intact along with it. Division of an invaded nerve beyond the limits of invasion may askild recurrence while division through an invaded part of the nerve is almost certain to be followed by recurrence. That this may not follow invariably

reviewed the previous reports of Badal and Lagrange, and Emanuel of similar tumours, and he fully discussed the close kinship of these growths with the retinal "gliomas", concluding that in neither group are the tumours gliomas but that they both consist of embryonic retinal tissue with appropriate regional differences

One of the most remarkable, as well as one of the most beautifully depicted, examples of diktyomi since Fuchs's review, is that described by Spicer and Greeves. This tumour occurred in a male infant who developed "seven clear, transparent bladders or cysts floating in the aqueous. They moved freely and rebounded from each other or from the walls of the anterior chamber just like toy balloons." These cysts had thin nearly transparent walls, the largest was about 3 millimetres in diameter, and two of them gave off lateral buds. The eve was removed and many more cysts were found between the iris and lens and in the vitreous. These had arisen from a solid growth of the chiary body, which contained rosettes identical in appearance with those of a retinal "glioma". The walls of the detached cysts had a microscopic structure perfectly simulating that of the embryone retina.

As both Verhoeff and Fuchs pointed out, diktyomas are undoubtedly closely related to retinoblastomas. They are to the pars ciliaris retinae what the retino blastomas are to the pars optica. Fuchs noted that the pars ciliaris still consists of immuture cells in the sixth month of foetal life, when the pars optica is well differentiated. He also cited an observation of Helfreich's (1875), who, in the eye of a child of 1½ with a retinal 'ghoma', saw also membraneous structures in the ciliary region composed of embryonic cells like those seen in diktyomas. It is also significant that rosettes like those of retinoblastomas may occur in diktyomas as in the case of Spiecer and Greeves already eited.

(3) Malignant ciliary epithelial tumours

These are rather variable in structure, but sub division of the group at originally suggested by Fuchs, serves no useful purpose. These tumours occur chiefly in adults, especially in eyes which have suffered previous inflammatory and degenerative changes. Growth is usually slow, but eventually the eye may be filled and its coats infiltrated. Metastries have not been described. In addition to the cases reviewed and described by Fuchs, examples subsequently reported which illustrate the variety of these tumours include those of Greeves, Meller, Hine and Barrow and Stallard. Microscopically the tumours consist of cubical or columnar epithelial cells, pigmented or unpigmented, arranged in various papillary, tubular, convoluted or reticulated patterns. In many cases the cells resemble those of the ciliary epithelium, from which the tumours clearly take origin. Fuchs a case was remarkable in several respects, the partly pigmented growths were multiple, arising not only in an annular manner from the ciliary body but also from the pigment epithelium of the retina at several points, and the old inflamed eye contained also masses of metaphistic bone, which were millitrated by the growths

RARE RETINAL TUMOURS OF OTHER LINDS

There occur occasional intra ocular growths of retinal or ciliary origin which cannot be placed with certainty in any of the preceding groups. Thus Alling

tangle of asteroid and fusiform cells with abundant fibrillary processes, the asteroid cells varying greatly in size and often containing multiple nuclei. Van Greson's stain showed collagenous tissue only around the few small blood vessels which entered the tumour the tumour fibres all stained yellow. Two patches of granular calcification were present. This specimen resembled in many respects the tumour studied by McLean, from the macular region of a woman aged 23. In McLean s case however, the growth replaced the inner layers of the retina leaving the external limiting membrane and the rods and cones intact, and it consisted largely of fusiform neuroglial cells with long fibrillar processes.

Both the clinical progress and microscopic structure of these tumours show relatively benign characters they have been slowly growing and highly differentiated, and they have not metastasized or recurred. However, the number of reported cases is so small that we cannot yet decide what range of structure and behaviour tumours of this kind may display

To be distinguished from true retinal gliomas are occasional cases of massive tumour like gliosis of the retina resulting from long standing inflammatory or degenerative disease e.g. that described by Friedenwald. We must also distinguish from primary retinal tumours extensions into the optic disc from gliomas of the optic nerve.

EPITHELIAL TUMOURS OF THE CILIARY BODY AND IRIS

Tumours of the pars ciliaris and pars indica retinae or of their embryonic precursors are exceedingly rare. In his classical paper on the subject in 1908 Fuchs divided these into beingn and malignant types and the latter into two sub-groups according to whether the growths consisted of embryonic or adult ciliary tissue and this classification has remained a satisfactory one

(1) The benign tumours of the citiary epithelium

Often called adenomas', these consist of tiny well defined nodules often more than I milimeter in diameter composed of cells resembling and electrly derived from those of the unpigmented layer of the cultary epithelium and occurring in the eyes of middle aged or old people. They may be not true tumours but rather focal hyperplasias related to sende changes but they may also be related to the progressively growing tumours of the ciliary epithelium to be described presently. A typical specimen is that reported by Velhagen

(2) Diktyoma

This is Fuchs a fame for a distinctive group of ciliary tumours occurring in children and consisting of tissue resembling embryonic retina. The tumour usually grows slowly infiltrates the cibary body appeads over the posterior surface of the iris and may invade the anterior chamber or massively fill the eye. Although the tumour is locally destructive metastases have not been observed, and enucleation of the eye is curative.

The most valuable of the earlier reports is that of Verhoeff who fully described a chary tumour from a child aged 21 the tumour had pedunculated globular excrescences which resembled luttle optic vesicles. Verhoeff also

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described a large ciliary growth in a boy 4 years old which consisted of a network of epithelial cells and islands of cartilage. Knapp and Verhoeff were of the opinion that it differed from the epithelial tumours of the ciliary region and called it an 'endothelioma on what grounds it is not clear. The photo graphs suggest a diktyoma, and the presence of cartilage in such a tumour would be no more surprising than in an embryonic tumour of the kidney or liver

Schuster described a heavily pigmented tumour in the eye of a woman need 32 with extension along the optic nerve, metastatic deposits on the surface of the cerebellum and in the spinal theea, and with metastases also in the liver and many lymph glands Microscopic examination showed a pigmented epithelial growth with gland like orientation of its cells, the epithelial character of which was most evident in the metastases. The tumour was interpreted probably correctly, as having arisen from the pigmented retinal epithelium. If this was so, the tumour was then allied to the malignant ciliary tumours just described (see especially Fuchs's case) but was unique in having extended outside the globe and in having produced metastases

Orton and I have described a retinal tumour of peculiar structure from a woman aged 79 This nearly filled the vitreal cavity, and consisted of bands of clongated cells with their long axes transversely across the bands and with processes attached to the connective tissues on either side. These characters led to the conclusion that the tumour had arisen from the radial fibres of Muller and was distinct from the astrocytic gliomas of the retina

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depicted by Dawson, and was succinctly epitomized by Nicholson (1922) as follows

"A young mole is covered by epidermis, with highly irregular, elongated and branched papiliae. The columnar basal cells, and to a lesser extent all those of the rete Malpighu are often deeply pigmented, especially in the deep parts of the papiliae. The hair follicles, sebaceous and sweat glands, if present, participate in the changes. The basal cells have a marked tendency to become loosened and to pass into the corium, becoming detached from the epidermis. This is usually most clearly apparent at the apices of the papillae. But this loss of cohesion occurs within the substance of the papillae as well, nests of oval or round cells with relatively small, darkly stained nuclei and homogeneous "glassy" cytoplasm



Fig. 443 —Pigmented mole of arm of a girl aged 8 showing papillary structure, frayed epidermis and masses of naevus cells (Deeper parts of dermis showed neurofibromatoid changes) (y. 40)

resulting These are the navvus cells. They are generally more or less deeply pigmented. They he loosely side by side, and are no longer organically connected with each other by prickles. The nests of navvus cells are at first entirely intra epithelial. Sooner or later, however, their epithelial covering gives way on the deep aspect of the papilla, and they are then partly surrounded by connective tissue. Fresh nests are constantly produced, and the old ones pass more and more deeply into the corium. They enter the tissue spaces of the corium and form irregular columns, which have usually lost their connections with the epidermis Mahy of these loosened epidermal cells do not assume the characteristic form described, but are oval, flat or branched. Multimucleated giant cells are not uncommon. Depigmentation constantly takes place, the pigment being taken up and removed by leucocytes and the fixed cells of the corium, so that old quiescent moles often contain little or no pigment, except generally in the basal

CHAPTER 58

THE MELANOMATA

means only melanin pigmented tumour Much of the confusion regarding the histogenesis of such tumours has arisen from supposing them all to be of similar origin-all mesodermal all epithelial or all neuro ectodermal. Let us, at the outset abandon this assumption and consider separately the several groups of melanotic tumours according to their sites of origin. The principal of these in mammals are the skin, the eye and the lepto meninges There is no reason to suppose that normal melanin production in these three main sites and in some subsidiary ones (e.g. certain nerve cells) is subserved by cells of similar nature or origin. The basal cells of the epidermis, the pigmented epithelium of the retina the dendritie pigment cells of the choroid and of the meninges, and the nerve cells of the substantia nigra, have no close affinity yet they are all melanin producers. Clearly then we should consider the melanomas of the various tissues separately from each other, and not force them artificially together in accordance with this or that hypothesis regarding the specificity of melanoblasts' 'Melanoblasts' are not cells of a specific type but are of as many and diverse kinds as there are different tissues capable of producing melanin Consequently, melanoblastomas 'are not tumours all of one specific type, but show a corresponding diversity. Those who are interested in the attempts of Ribbert and others to interpret all melanomas as derived from specific "melanoblasts (Ribbert called them 'chromatophores') will find them well set forth and critically examined in J W Dawson's classical monograph

We will discuss melanomas under the following headings

- Melanomas of the skin
 - 2 Melanomas of juxta-cutaneous mucous membranes
 - 3 Intra ocular melanomas
- 4 Meningeal melanosis and melanomas
- 5 Melanomas of other tissues
- 6 Melanomas in animals
- 7 General conclusions

MELANOMAS OF THE SKIN

(1) The pigmented mole or naesus

The common pigmented mole or naesus is not a tumour but a malformation But, since nearly all cutaneous melanomas arise in pre-existing moles the structure of these affords the essential clue to the histogenesis of the tumours. Pigmented moles are probably always congenital with rare exceptions they are discovered at birth or soon after. They show a definite life history comprising an early period of active development in childhood a stage of quiescence in early adult life and thereafter a stage of atrophy. Only in the first period in children is their mode of origin apparent. This was studied in great deful and beautifulty

containing abundant clusters of small naevus cells mainly unpigmented quite detached from the epidermis and lying in thickened fibrotic dermis (Fig. 446). The deeper parts



Fig. 445—Papillary pigmented mole of back of girl aged 18 showing clusters of naevus cells detached from epidermis. (× 120)



Fig. 446—Case I Detached clumps of naeyus cells in dermal papillae and deeply pigmented epidermis (× 120)

of the lesion consisted of whorfs and bundles of cellular fibroblastic tissue similar to that of the bengin lesions of neurofibromatosis and clearly related to the cultaneous nerves (Fig. 447). In places there was an immate admixture of neurofibromationd whorfs and cells of their epithelial papillae Moles often persist in this state for long periods of time Sooner or later, however the naevus cells disappear and the corum between the epidermal papillae then consists of a dense connective tissue?

I cannot understand how any histopathologist who has examined young moles in their early formative stage can fail to endorse Dawson's and Nicholson's descriptions and to agree with their conclusion that naevus cells are detached epidermal cells. This seems to me to be too obvious for argument. The structure of young moles shows plainly that the naevus cells do not take origin from the sheaths of nerves or any other dermal elements but from the epidermis and the epidermis only



Fig. 444 —Detail of Fig. 443 showing identity of frajed epidermal and naevus cells. (× 120

To Nicholson's summary just cited I would add that some young moles show the development of naevus cells not as isolated nests in the epidermis but as a general loosening and detachment of the entire basal-c ll layer. An example of this from a child aged 8 is depicted in Figs. 443 and 444 in which the identity of their yabundant naevus cells with frayed out epidermis is obvious. Examples of moles from older subjects after completion of genesis of the naevus cells and when these are now quite detached from the epidermis are depicted in Figs. 445-447. The history and structure of one of these are worthy of note.

Case I — A woman aged 29 complained that since childhood she had had a small black mole of the skin of the mid-dersal region. At lifter this had been flat, but later it enlarged slowly and became raised above the surface until at the age of 20 it was as large as a supence still smooth and black. Thereafter it continued to enlarge but its colour became lighter. When excised it was a well-crummented raised brown plaque 2 continueters in diameter with a corrugated surface. The patient had no signs of any other skin lesions or other physical abnormalities. Hintil via—The structure was mainly that of a typical moderately populary benign pigmented mole clothed by pigmented cyndemis and

are nerves and nerve endings, so that it is not surprising to find these involved in the anomalous field of tissue

(2) The epithchal histogenesis of melanomas of the skin

With few exceptions, cutaneous melanomas arise from pre-existing moles While the structure of young pigmented moles shows plainly the epidermal origin of the nacyus cells, that of carly malignant melanomas shows equally plainly their origin from nacyus cells and from the endermis itself. That the tumours take origin from naevus cells is not questioned even by those who suppose these to be of non epithelial neural origin, all stages in the transformation of naevus cells to malignant melanoma cells are often demonstrable. But the naevus cells are not the only source of the tumours, as Dawson and Nicholson (1923) showed. there is clear evidence of progressive tumour genesis from the basal cells of the epidermis also A mole becomes malignant by cancerous conversion of already formed naevus cells, and also in many cases by the simultaneous splitting off from the epidermis of new broods of neoplastic naevus cells. Nicholson depicted a striking example of this process and rightly insisted that the appearances cannot be explained away as due to secondary infiltration of the epidermis The change is plainly in the conderms itself, whence the melanomatous cells proceed to invade the dermis

Those who doubt the epidermal origin of the cutaneous melanomas point out that these tumours show no signs of epidermal differentiation, i.e prickle cells and corrufcation. To which the reply is (a) that the same might be said of most basal cell carcinomas of the skin, (b) that, just as pigment formation is much more active in the basal cells of the epidermis than in its spinous and more superficial cells, so in a tumour the assumption by the cells of predominant pigment formative functions may well be accompanied by loss of the capacity for orderly epidermoid differentiation, and (c) there do occur occasional tumours which are both melanotic and epidermic, namely pigmented basal cell and squamous cell carcinomas (Bonser). May not these pigmented basal cell and squamous cell growths be the very "missing links" between the ordinary skin carcinomas on the one hand and the melanomas proper on the other? The fact that such tumours behave more like skin carcinomas than like melanomas is not very surprising. And surely the very custence of pigmented epidermoid growths of this Find points to the epithelial non neural origin of integumentary melanou and 1980 facto of integumentary melanous tumours.

It remains to add here certain other relevant facts. Bloch's "dopa" reaction a test for the presence of an intra cellular melanogen oxydase (well summarized by Spencer, Dawson Laidlaw, and Dawson et al) is given in common by the basal cells of the epidermis, those of hair foliacles naevus cells and malignant melanoma cells. In foctal and infant skin visible melanin appears first of all in the basal cells of the epidermis, and Bloch's test shows that prior to the development of visible pigment these cells and these cells only, are 'dopa' positive. These facts accord with the purely epithelial origin of skin melanin and of skin tumours producing melanin.

nacyus-cell clumps but the two kinds of cells could everywhere be distinguished easily and there were no transitions between them

J This case introduces us to the association first noticed by Soldan and later stressed by Masson of pigmented moles with local neurofibromatoid changes When searched for, distinct though often slight signs of dermal neuro fibromatoid change can be found in a large proportion—perhaps the majority—of raised pigmented moles, and abundant nerve fibrils have been shown to traverse this tissue and to come into close relationship to the naevus-cell clumps (It is necessary to add that some writers have certainly over-estimated the number of nerve fibres present and their intimacy with the naevus cells. The silver impregnation methods used are not as specific as is often supposed and impregnated collagen and reticulin fibres have undoubtedly been mis identified as nerve fibres.



Fig. 447 - Case 1 Neurofibromatoid tissue adjacent to a deep sebaceous gland (120)

I find most of Masson's and Foot's figures uncommeng in this respect indeed. I think many of them show plainly that the supposed nerve fibres were connective tissue fibres.)

We will return presently to discussion of the neural relationships of pigmented moles and tumours. But I must anticipate this liere by stating that it my view, when abnormalities of nerves are found in a mole these are merely a part of the malformation. The developmental disturbance producing a mole affects fill of the constituent tissues in the disturbed field of skin. In addition to the hyper pigmentition evageerated papillation nacture-cell formation and associated neurofibromatoid changes which we have considered moles my show also great increase in the number and size of hairs and hair follicles or increase of blood vessels giving angiomatous characters. I agree with Disson. Innes and Harvey that the pigmented mole is a complex malformation. I minifestation of disturbed development of all ingredients of the skin. Amongst these ingredients

constituted about 4 per cent of skin and lip cancers I encountered 9 cases of cutaneous melanoma in approximately 1,200 cancer necropsies

(b) Age and sex

Melanomas occur at all ages, about three quarters of them develop between the ages of 30 and 70, but without special prominence in any particular decade (Affleck, Webster et al) They are rare in young children. Of peculiar interest are cases, like that reported by Weber et al, in which disseminated melanoma is transferred from mother to infant in the muero. Males and females are about equally liable to melanoma.

(c) Site

No region is exempt, but the commonest sites are the head and neck, trunk and genitalia, and the feet Except for the feet, the least frequent sites are the limbs, especially the hands (Peller, Webster et al.)

(d) Race

It has often been stated that dark-skinned races are relatively exempt from melanoma, but I can find no sound evidence for this impression. The disease has often been observed in Negroes (Bishop, Webster et al), and Hewer reported 47 cases in Sudanese, in whom melanomas of the feet are relatively common.

(e) Pre existing moles

These are recorded in the majority of eases, e.g. in 65 per cent in the series of Webster et al and 84 per cent of Affleck's series. Since, in some cases small moles have certainly been forgotten or overlooked, the actual proportion of melanomas preceded by moles must be even higher than this

(f) Intury

Caution is always needed in attributing a causative roll to injury in the genesis of tumours but there are good grounds for believing injury to play a definite part in the causation of melanomas. These grounds are as follows

- (i) In cases of melanoma supervening on a mole there is often a history of mechanical myury or of mecomplete surgical removal, eg m 36 of 68 cases recorded by Webster et al. Of course, it is often not possible to be sure that the supposed irritation or attempted removal of the mole was not the result rather than the cause of the supervention of malignant change.
- (ii) In a considerable proportion of cases of melanoma of the foot or leg there is no history of previous mole, but on the contrary a history suggestive of injury Of Hewer s 47 melanomas in Sudanese 60 per cent were on the feet and a further 15 per cent on the legs, and Hewer suggested trauma as causative Sub ungual melanomas are often not preceded by recognized moles, and the suggestion that trauma can be causative is at least plausible I have seen a fatal melanoma arising without a pre existing mole on the toe of a tile worker whose occupation involved long

- (3) Objections to the hypothesis of neural origin of moles and melanomas of the skin
 - (a) The main objection is that these lesions are as already insisted plainly of epidermal origin
 - (b) The resemblance of some groups of melanoma cells to groups of Merkel Ranvier cells or Wagner Messarer corpuscles does not justify far reaching histogenetic conclusions. The shapes and mode of arrangement of the cells of malignant melanomas are very diverse and simulation of cell aggregates of many kinds can be found in them.
 - (c) Too much has been made of the association of pigmented moles with neurofibromatoid changes and of the hyperneuria of some moles. As already stated I look upon these as merely part of the malformation, and whatever the relationship between the abnormal epithelial and neural tissues in the malformed area it still remains true that the pigmentation is in the former and not in the latter. It is quite possible that the formation of a pigmented mole may depend primarily on a disturbance of innervation that it may be primarily an area of malformed sensory end organs but if so its excessive pigmentation and the pigmented tumour which may spring from it are still epithelial in origin.
 - (d) Normal neural sheath cells and sensory end organs are unpigmented and tumours known to arise from them—neurilemmomas and neurofibromas are unpigmented. If cutaneous melanomas were of neural sheath origin it is strange that they should be the only lesions in which cells of this lineage acquire pigment formative functions.
 - (e) Feyrter recognizing the objections to the hypothesis that Schwann cells are the source of naevus cells supposes these to come from certain special neuro-endothelial cells which are situated in nerve sheaths and which extend (as Masson's clear cells Kromayer's vesicular cells or Langerhan's cells) into the epidermis and he proposes to call naevi neuro-endotheliomas. This alias answers none of the foregoing objections

There is of course one sense in which the neural hypothesis is compatible with the epidermal origin of naevi and melanomas. In so far as the epidermis is itself a sensory end organ its cells are neural. Free nerve terminals ramify in the epidermis and it is believed that the cells of Merkel Ranvier are themselves modified epidermal cells. Is it possible that the dermal sensory corpuseles also may contain epidermal cells split off from the epidermis during development? Is the splitting off and itsolation of naevus cells an evaggeration of a normal process in the development of the sensory apparatus of the skin?

(4) Incidence and causation of melanomas of the skin

(a) Frequency

Fortunately melanoma is a relatively rure disease. Most people have one or more pigmented moles, and only an infinitesimal fraction of the total number of these will produce melanomas. However, since almost all melanomas do arise in moles removal of these especially when they are of such a size or site that they are liable to injury is a wise precaution. Peller estimated that melanomas

metastatic spheroidal-ceiled carcinoma. The patient then volunteered the information that a small brown mole had been excised from the same site 2 years previously

Stout has reviewed examples of what appears to be intra epidermal amelanotic melanoma

(6) The spread and metastasis of cutaneous melanoma

The behaviour of no other tumour is so unpredictable as that of melanoma A 'mole' unsuspected of malignancy or so small as to be overlooked may produce widespread rapidly fatal metastases. Or a 'mole' may have been removed and all but forgotten 5 or 10 or more years before disseminated melano matosis develops. Or, rarely, a frankly malignant growth for which a bad prognosis is given is unexpectedly cured by excision. Or, more rarely still, a melanoma which has already metastasized undergoes spontaneous retrogression.

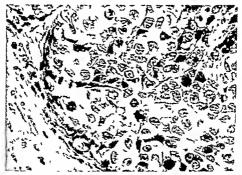


Fig. 449—Amelanotic part of recurrent melanoms of calf of leg which recurred 4 years after apparently successful radium treatment of initial growth. Note mitotic figures. (× 400)

For examples of these and other anomalies of behaviour, see my 1934 work, and the papers of Wilbur and Hartman, Selig, Temple, and Webster et al. Fig 449 depicts a tumour which exhibited long delayed local recurrence

The mode of dissemination of a particular tumour is equally unpredictable tumours spread to surrounding parts via lymphatics and produce satellite tumours in the immediate neighbourhood or along the course of the main lymph atics. Others, while showing little spread locally, produce early metastases in the regional lymph glands (Fig. 450). Others fail to metastasize by lymphatic routes but disseminate solely by the blood-stream. Blood borne metastases may develop in every organ and tissue of the body, or in one or two sites only, or there may be widespread dissemination yet with anomalous exemption of one or more man organs such as the liver or brain. Cerebral metastases or intestinal metastases.

standing on a hot floor I have also seen a melanoma which had arisen without evidence of a previous mole at the margin of a chronic various ulcer

'(iii) The development of melanomas in mice and dogs following prolonged tarring is referred to in Chapter 4

(5) The structure of melanomas of the skin

Dawson's beautifully illustrated work renders it unnecessary to repeat in detail the histopathology of these growths. It must suffice here to state that their structure is very diverse—that their eells may be spherical polyhedral, fusiform or pleomorphic—that they may be arranged in epithelium like clumps, or in prominent perivascular mantles, or quite diffusely—that they may



be deeply pigmented or unpigmented or may show pigmented and unpigmented cells in close contiguity—and that 1 single tumour sometimes shows many or all of these structural variants. (See Figs 448-451)

Great experience is necessary in the microscopical diagnosis of early malignant change in pigmented moles. Suspicious features are increase in the size of the nice and cytoplasm of the naexus-cells cellular pleomorphism, mitotic figures the invasion of the overlying epidermis by groups of atypical cells and unequal distribution of intra-cellular pigment in different parts of the suspicious areas

Amelanotic melanoma can cause great diagnostic difficulty as in the following

Case 11—I or 9 months a man aged 36 had noticed an enlarging subcutaneous tumour of his calf. This was excised, it was a fairly well-defined white growth I centime rest in diameter bying in the derims and subcutaneous time. The endermis was unaffected Microscopically it presented the appearance shown in Fig. 443 and was diagnosed as

(7) A note on "blue nacy1"

The Jadassohn Ticche ' blue naevus ', well described by Montgomery and Kahler, must be distinguished both clinically and histologically from the ordinary pigmented moles and melanomas. It is almost always concenital, it is situated most frequently on the face, forearms or hands, and less frequently on the trunk or lower limbs, it appears as a well circumscribed circular or oval, firm, blue or bluish black papule, usually only a few milimetres in diameter, it usually remains unchanged for life, except for gradual fibrosis with age in some cases. and the risk of supervening tumour is negligible. Microscopically, long fusitorm, strap-like or branched melanin laden cells are found scattered diffusely or in irregular masses in the deeper parts of the dermis According to Montgomery and Kahler, these cells show no special relationship to nerves superficial parts of the dermis and the epidermis are normal, and the little mal formation appears to be quite distinct from the ordinary piemented mole, though the two occasionally coexist. The nature of the pigmented cells is undetermined, most workers suppose them to be mesenchymal They are "dopa" positive, and appear to be identical with the so called "Mongol cells", which occur in the dermis over the sacrum and back and which are regarded as mesenchymal melanoblasts (Laidlaw) Montgomery and Kahler distinguish between "blue naevus" and 'Mongolian spot', the latter usually a poorly defined brownish area in the skin over the sacrum, present at birth and tending to disappear later, but microscopically the two are somewhat similar

MELANOMAS OF JUYTA CUTANEOUS MUCOUS MEMBRANES

Primary melanomas are reported occasionally from the nasal cavity, mouth (New and Hausel, Gotschalk et al), conjunctiva or episcleral tissues (Dawson Duke Elder), rectum, and vagina or cervix (Taylor and Tuttle, Bromberg and Brzezinski) Needless to say, care must be exercised not to mistake secondary for primary growths in these and other unusual situations but there is no doubt that primary melanomas can arise in the juxta cutaneous mucous membranes In most cases the histogenesis of these tumours is almost certainly the same as those of the cutaneous ones, i.e. from melanoblastic epithe lium like that of the epidermis In some cases this epithelium may actually be developmentally heterotopic epidermis, for we know that hairy 'naevi" can occur in the conjunctiva and in the oral mucosa But we need not always postulate a developmental heterotopia, for epidermal structures can be acquired by meta plasia, in the vagina and eervix uters at least Thus Nicholson (1918 and 1936) has described the development of sebaceous glands, hairs and a pigmented mole in this situation, and I also (1936) have recorded the metaplastic formation of hairs in an endocervical polypus It is quite probable, too, that the juxta cutaneous epithelia normally possess pigment formative capacities in slight degree witness their pigmentation in Addison s disease, etc

Many mammals, of course show heavy pigmentation of their oral mucosac,

e g d fferent breeds of dogs vary greatly in this respect

It is certain that the epibulbar melanomas are not always of conjunctival epithelial origin for epibulbar pigmentation elearly similar to meningeal pigmentation and unrelated to the conjunctival epithelium, certainly occurs

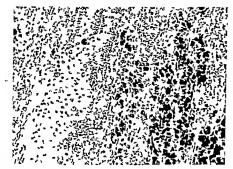


Fig. 450—Metastatic round-celled melanoma in inguinal lymph glands a mass 4 centimetres in diameter which appeared a year after amputation of the with a Blood blister in a woman aged 60. Note groups of heavily pigmented and unpigmented tumour cells side by side (x 150).

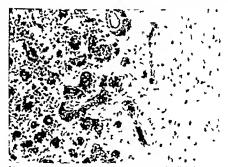


FIG. 451—Metastatic melanoma of brain (Case NVIII of Trinca and Willis) showing perivascular spaces infiltrated by heavily pigmented cells. (× 150)

from unsuspected primary growths have caused many diagnostic errors (Willis 1934 Trinca and Willis 1936 and Fig 451) Metastases often develop in unusual sixes e.g. mucous membranes endocardium testis or placenta it is true that in structure and behaviour the ocular melanomas show general resemblances to the cutaneous ones, we must not ignore their differences. Spindle celled structure is much more prominent in the ocular tumours, which also show decided differences from the cutaneous ones in their metastatic propensities. Ocular melanoma produces remarkably frequent and often long delayed metastases in the liver, and it seldom effects widespread dissemination in almost every tissue of the body, as cutaneous melanoma often does. These differences should warn against over-zeal in attempting to formulate a common histogenesis for the ocular and cutaneous tumours. And, after all, the skin is not the retina and choroid—and the pigmented tumours of the two may be comparable in nothing save their pigmentation.

(2) Incidence and causation

Intra ocular melanomas, which are relatively rare tumours, occur about equally in the two sexes. Children are rarely victims. Terry and Johns found the highest numbers of cases in the fifth and sixth decades, and Duke Elder estimated the mean age to be 50. The tumours arise in any part of the choroid, ciliary body or aris, and are most frequent in the posterior half of the globe. Save that some of them appear to arise from pre-existing beingin pigment spots in the choroid, nothing is known of their causation. An hereditary predisposition is sometimes suggested, but acceptable instances are exceedingly rare (Duke-Elder). The evidence that previous injury or inflammatory disease predisposes to mela nomas is inconclusive. They are often unsuspected and undiagnosed, e.g. in 42 of the 94 cases reported by Terry and Johns.

(3) Structure

Little need be said of this Diffuse or fascicular spindle celled structure is the commonest, rounded or polyhedral celled cpithelioid structure is less frequent, and combinations and transitions between the two are often to be found. Most of the tumours are heavily pigmented, some of them so heavily that all cell details are hidden by the pigment. The degree of pigmentation often differs in different parts of the growths, especially in metastases, but complete absence of pigment is rare.

(4) Spread and metastasis

Extra bulbar extension is most often trans scleral, around the perforating vessels, and less often via the optic nerve. A greater risk, however, is metastatis by the blood stream. This often takes place from small tumours still confined within the globe and in some cases unsuspected.

Metastases may develop in any organ, and may not make their appearance for years after apparently successful removal of the eye Prognosis is thus very uncert in Mori recorded the development of widespread metastases 15 years after removal of the eye, Cairns saw orbital recurrence and a large metastasis in the scap tula 18 years after enucleation of the eye, the interval between enucleation and the 18 years after enucleation of the eye, the interval between enucleation and mad MelicLeod, in H G W Dawson's case subcutaneous and ovarian metastases was 18 years after removal of the eye, and Elsberg recorded spinal metastases

(see Case III below) and some epibulbar tumours arise far back on the selera and well away from the conjunctiva

INTRA OCULAR MELANOMAS

(For a good general account of the incidence, structure and behaviour of these see Duke Elder)

(1) Histogenesis

In my opinion, the histogenesis of the melanomas of the useal tract is still unsettled. There are three hypotheses as follows

(a) The hypothesis of epithelial origin

In favour of this hypothesis are the facts that in the embryonic eye melanin develops in the pigment-epithelium of the retina long before it appears in the choroid that the retinal epithelial cells are the only ones in the eye to give a positive dopa reaction at any stage of development, that there are substantial grounds for believing some malignant melanomas to arise from pre-evisting benign choroidal pigment spots or moles' that the structure of these moles' is compatible with the idea that their cells may be split-off retinal epithelial cells analogous with naevus cells in the skin and that there is a general similarity of structure between the intra-ocular melanomas and the culaneous ones. Some upholders of the epithelial view have supposed that the cells of the choroid are mesenchymal but receive their pigment from the retina. Others however, like Dawson believe that the dendritie pigment-cells of the choroid may be, not merely chromatophores which have received pigment from the retinal epithelium, but actually migrated cells of that epithelium.

(b) The hypothesis of mesenchimal origin

This is supported by the homology of the choroid and leptomeninges by the close re-emblances to each other of the branched pigmented cells of these two membranes by the absence of histological evidence that the choroidal pigment is transferred from the retina or that the choroidal cells are derived from the retinal epithelium but that on the contrary they appear to be ab inno choroidal cells which develop pigment independently of the retina (Mann)

(c) Masson's hypothesis of nerve sheath origin

Masson's hypothesis was introduced in reference to the eutaneous melanomas only and even assuming that it were true for the skin tumours its extension (by Duke Elder and many others) to embrace the intra ocular growth is well appears to me to be unwarranted. As far as we know the choroid contains no sensory end-organs at all corresponding to the Merkel Ranvier cells or Messing corpuscles to which in Masson's view the cutaneous melanomas are related

I find myself unable to decide between hypotheses (a) and (b) Further work is needed on the embryological histology of the eye more must be learnt of the structure and mode of origin of the benign naevi or moles of the useal tract from which it seems elear some melanomas arise (Collins Houwer Johnston Albers) and of early melanomatous changes in previously normal eyes. While

both the brain and dura mater and invading the superior longitudinal sinus. A few small brown or black spots were present on neighbouring parts of the cerebral surface. The pia mater of the base of the brain, especially the frontal lobes showed extensive patches of grey pigmentation. The rest of the brain and its coverings were normal. Patches of slight brown pigmentation were present in the skin of the right side of the face and temporal area. The whole of the outer surface of the sclera of the right eye showed prominent brown patches and there was slight similar pigmentation of the left sclera. The intra ocular structures appeared normal. Except for pneumonia and multiple benign uterini, myomas all the viscera were normal and careful search failed to disclose a primary melanomia or a scar of the skin. Histology—The tumour consisted of diffus ly arranged heavily pigmented fusiform and rounded cells which invaded the dura mater and bruin tissue (Fig. 453). The pigmented patches in the pia mater contained many elongated pigment-cells resembling those of Fig. 452 and the episcleral pigment patches showed similar cells.



Fig. 453—Case III M= main mass of growth on brain surface B= brain with heavily pigmented tumour infiltrating perivascular spaces (\times 60)

This case is of special interest in showing not only an undoubtedly primary malignant melanoma of the meninges, but also associated melanosis of the meninges and (presumably) non epithelial melanosis of the epibulbar tissues and possibly of the skin also on the same side Ordinary naevi of the skin were not present, but in some other eases extensive melanosis or melanomatosis of the meninges has been associated with multiple or widespread pigmented moles of the skin also (Grahl, Schopper, Lua, Maclachlan, Berblinger, Heilmann, Bjorneboe)

It is a notable fact that in none of the cases of indubitably primary melanotic tumours of the central nervous system have viseeral metastases been found. In this respect the behaviour of meningeal melanomas differs strikingly from that of eutaneous and ocular ones a difference which favours the view that they differ histogenetically. When, as in cases described by Hassin and Bassoc and by Foot and Zeek, supposedly primary melanomas of the brain or meninges have been

after an interval of 14 years Wilbur and Hartman reported 3 cases, each with metastases in the liver and subcutaneous tissues which appeared after intervals of 13 10 and 10 years respectively following removal of the eye. These writers referred also to other examples of long delayed metastasis the longest interval being 32 years in Wilder's case.



Fig. 452—Normal meningeal pigment cells in a cleared lightly haematoxylin stained strip of pia mater from a Chinese male aged 37 \times 100)

The liver is the favourite site of metastasis and may attain a huge size Rolleston found the average weight of the liver in 22 collected cases of ocular metanoma with hepatic metastases to be 6 000 grammes. Hamburger recorded a liver weight of 10 000 grammes and I one of 7 850 grammes (1934 Case 117)

MENINGEAL MELANOSIS AND MELANOMAS

Elongated and branched pigment-cells are normally present in the pia mitter especially of the bits of the brain stem and especially in the dark skinned and Mongolian peoples (Fig. 452). The origin of these cells developmentally is uncertain the view often expressed (hoping to unify histogenetic concepts of all groups of melanomas) that they are of neuro-epithelial origin is only supposition they may equally well be mesenchymal. They are certainly the source of diffuse melanosis and primary diffuse or focal melanotic tumours of the meninges and central nervous system. Acceptable eases of this kind include those of Virchow (1859). Mincilli, Hirschberg, Bott. Kawashuma. Schopper, Lun. Kiel. Omodei. Zotini, Kraft. Dieckmann, Heimann. Björneboe and Akeliutis. and the following is an additional example.

Case III North pix on a woman aged 46 who had had recent signs of cerebral tumour dished the following abnormalities. At the upper medial border of the right cerebral beauty-here there has an arregular black tumour 4 certimetree in diameter; fitting

of melanotic tumours. The origin of the pigment cells of the meninges, from which primary meningeal melanomas arise, is undetermined, there is no evidence that they are derived from neuro epithelium or that they are not mesenchymal, and the meningeal tumours behave differently from cutaneous and ocular ones. The histogenesis of the choroidal pigment cells and of the intra ocular melanotic tumours is still unsettled, it is possible that they may be derived from the pigmented layer of the retina, or from the mesenchyme of the choroid which is the homologue of the meninges, or from either. Some epibulbar melanomas almost certainly arise from non epithelial episcleral pigment cells comparable with those of the meninges, but conjunctival epithelial naevus cell melanomas also occur.

I conclude, as I began, by saying that I think it a mistake to regard all melanotic tumours as comparable and to try to devise a unified histogenetic hypothesis to embrace them all. Their several tissues of origin differ greatly in development and function, and the corresponding several groups of tumours differ significantly from one another in structure and behaviour. It may be contended that the essential community of all pigmented tissues is shown by cases (such as my Case III, and those of Berblinger, Bjorneboe, and others) in which developmentally abnormal pigmentation affects skin, eyes and meninges simultaneously. This argument, strong though it appears to be, is not necessarily valid. If melanin production is merely a common function of several distinct kinds of tissues, then factors disturbing that function might well do so simultaneously in those several tissues—just as diabetes may cause visible disturbances of glycogen or lipoid metabolism in several distinct kinds of cells.

It is not impossible that further research may lead to some unification of our concepts of melanin formation and of the histogenetic relationships of melanotic cells and their tumours. At present, however, our knowledge is too incomplete to allow us to frame any unified hypothesis, and attempts to do so are forced and speculative.

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(A useful well illustrated account of the ocular melanomas)

accompanied by metastases in other parts, there is room for strong suspicion that a small primary growth of the skin or eye has cluded discovery or that (as in a case reported by Trinca and myself) a small skin lesion has been removed months or years previously and forgotten

MELANOMAS OF OTHER TISSUES

In my opinion the concluding sentence of the last paragraph applies also to most perhaps all, of the supposedly primary melanotic tumours of other viscera og those of the adrenals reported by Davidsohn Schmidt Goldzelier Maelachlan and Smith and that of the gall bladder reported by Rosenthal In such cases unless meticulous search of every part of the skin and eyes and juxta-cutaneous mucous membranes proves the absence of a possible primary growth there and inquiry clients positive certainty that the patient has never had any skin lesion which might have been the primary source the primary visceral origin of a melanoma cannot be accepted. I know of no reported cases fully satisfying these strict requirements

MELANOMAS IN ANIMALS

Cutaneous melanomas are well known in horses dogs cattle and pigs (Feldman) but have seldom been observed in other animals. Feldman refurred to one example in a eat. Orr and Polson saw one in a rabbit and melanotic tumours, some with a heritable tendency, occur also in fish (Haddow and Gordon and Smith) Old grey or white horses are peculiarly prone to eutaneous melanomas the commonest sites of which are about the base of the tail and the genitalia. These growths are apparently not preceded by benign moles comparable to the human ones Old dogs also frequently develop eutaneous melanotic growths these are sometimes benign multiple or single and some times malignant the malignant ones often arising in previously indolent growths of the benign type. The structure of the benign growths, however is unlike that of human pigmented moles consisting usually of projecting pedunculated masses clothed by intact heavily pigmented epidermis underlain by thickened dermis containing few or many rounded or elongated cells loaded with pigment many of them clearly only phagocytes Malignant growths show a diversity of structure and a capacity for metastasis similar to the human ones Feldman gives references to occasional instances of melanotic tumours of the meninges or brain in animals but whether primary or secondary is uncertain. I have not read of nn intra ocular melanoma in an animal

Closer study of melanosis and melanomas in animals is needed—it will surely help in the solution of some of the vexed problems of histogenesis in this field

GENERAL CONCLUSIONS

The views expressed above regarding the histogenesis of the several groups of melanomis may now be epitomized. In my opinion naevus cells and malignant melanomias of the skin are certainly of epidermal origin. this does not exclude the participation of nerves and nerve-endings in the malformation which a pigmented mole is nor the participation of taetile epidermal cells in the formation.

of melanotic tumours. The origin of the pigment cells of the meninges, from which primary meningeal midnomas arise, is undetermined, there is no evidence that they are derived from neuro epithelium or that they are not mesenchymal, and the meningeal tumours behave differently from cutaneous and ocular ones. The histogenesis of the choroidal pigment-cells and of the intra ocular melanotic tumours is still unsettled, it is possible that they may be derived from the pigmented layer of the retina, or from the mesenchyme of the choroid which is the homologue of the meninges, or from either. Some epibulbar melanomas almost certainly trise from non epithelial episeleral pigment-cells comparable with those of the meninges, but conjunctival epithelial nievus-cell melanomas also occur.

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CHAPTER 59

CHORDOMA

HISTORICAL OUTLINE

In 1857, several examples of small gelatinous masses projecting into the cranial cavity from the clivus were described by Luschka, Hasse, Zenker and Virchow Virchow regarded these as cartilaginous, and, because of the vacuolated character of their cells, named them "ecchondrosis physaliphora" H Muller recorded a careful study of the notochord in the developing skull, and expressed the view that the so called "ecchondroses' were really derived from notochordal remnants Subsequent writers, however, adhered to Virchow's view, and it was not until 1894 that confirmation of Muller's opinion was advanced by Ribbert Since then, it has been generally accepted that the gelatinous nodules occasionally found projecting from the clivus or dorsum sellae are "ecchordoses" consisting of heterotopic chordal tissue, and that true tumours, chordomas, arise from these or from the intra osseous remains of chordal tissue. The first recorded spheno occipital ecchondroses' large enough to cause symptoms were those of Klebs (1864) and Grahl (1903) the latter so large a mass that it probably was a chordoma The first crantal tumour specifically designated a chordoma' was that of Fischer and Steiner (1907) and the first record of project tion of such a tumour into the pharynx from the skull base was that of Linck (1909)

The first to report chordomas in the sacro cocygeal region were Feldmann (1910) and Mazzia (1910) and Mazzia (1910) although Morpurgo reported such a growth in an osteomalacic rat in 1907 although Morpurgo reported such a growth in an osteomalacic rat in 1907 and it soon became apparent that these were commoner than their eramal counterparts Chordomas of the vertebral column, the least frequent site, have been well recognized only recently (Cappell, 1928, Guthert, 1939) The most valuable reviews of the subject of chordoma are those of Stewart (1922), Stewart and Morin (1926), Cappell (1928), Guthert (1939) and Harvey and Dawson (1941) Other notworthy papers include those of Owen and co authors (on chordomas of the cervical vertebrae) and Hutton and Young

THE DEVELOPMENT OF THE NOTOCHORD

The correctness of Muiler s observations nearly a century ago on the development of the spheno occipital part of the notochord and its relation to ecchordoses has since been verified repeatedly Embryological studies show that the upper end of the young notochord closely approaches the inner surface of the sphenod and may lie in contact with the durd overlying the dorsum sellae, that more caudally in the basilar part of the developing occipital bone, the notochord approaches the lower or pharvingeal surface of the bone and part of it may he between the basilar plate and the wall of the pharyinx and that in any of these situations remnants of chordal tissue frequently persist in adults (Williams, Huber

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Microscopical examination (Fig. 455).

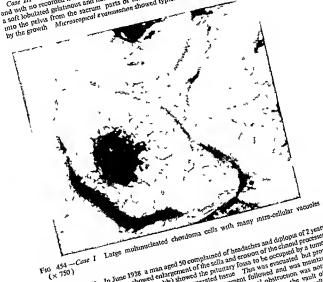
Microscopical examination (Fig. 455).

Microscopical examination (Fig. 455).

Microscopical examination (Fig. 455). The liver contained 3 small gelaunous metastases Microscopical examination (Fig. 455) showed typical chordoma with irregular clumps of vacuolated cells and plentful extracellular cures. Case III — Necrops) on an elderly woman who was admitted to hospital in extremis and monomous and monomous discincers in addition to fairly moderate and monomous and monomous discincers in addition to fairly moderate and monomous and monomous discincers. cellular mucus

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Newland and Woollard) That these remnants are the origin of ecchordoses, and of chordomas is clear to anyone familiar with them

The persistence of aberrant buds of notochordal tissue in the sacro cocygeal region also, described by a number of workers (e.g. Berard and co workers 1922 and Horwitz, 1941), can easily be verified in median and paramedian sections of this region in foetuses or infants, and there is little doubt that remnants of these are the source of sacro coccygeal chordomas. In the spinal column the rarest site of chordomas, aberrant chordal tissue has seldom been seen. It seems very probable then that the usual source of chordomas is from such aberrant residual tissue as we are familiar with at the two extremities of the axis, and rarely, if ever from the normal intervertebral dises

Ecchordoses

Ecchordo, es of the spheno-occipital region are not uncommon when earefully sought Ribbert claimed to have found them in 2 per cent of necropsics, and Stewart and Morin who reviewed 24 recorded examples, found 4 in 350 necropsies They were rather less frequent in my necropsy experience. I found 5 ecchordoses in over 1 000 necropsies in which they were looked for. They appear as soft gelatinous pedunculated masses usually only a few millimetres but sometimes 2 centimetres or more in diameter, often with flat inner surfaces where they have hin against the brain stem. The pedicle is often very narrow even filamentous. the little mass being moored loosely to the dorsum sellae by a thread. The pedicle which consists also of chordal tissue always transverses a small aperture in the dura mater and vertical sections through the aperture will show that the ecchordous is continuous with remnants of similar tissue in the bone. Microscopically an ecchordosis like the notochordal remains from which it springs consists of irregular vacuolated cells single or in aggregates set in an abundant mucoid matrix. Ecchordoses are quiescent chordal ectopias, and should be distinguished from true tumours to which however, they may give origin

FIVE PERSONALLY STUDIED CHORDOMAS

The following five personally studied cases of chordoma exemplify most of the features of this disease. Three of the timours were sacral one was cranial and one was upper thoracie in position.

Case I (Reported in 1930) —The tumour a huge sacral chordoma with massive extension into the thigh had produced symptoms for 4½ parts before the woman s death at the age of 41. Multiple existores of many bones had also been present since childhood. Accopty showed that the huge gelatinous, partly calcified sacral tumour which weighed 200 ounces had probably invaded the main tilac veins—and that there were multiple gelatinous metastaces in the lungs liver heart spleen kidneys thyroid and skin. Microscopical examination (Tig. 454)—The tumours consisted of prominently vacuolated cells with many multinucleated grant forms, and abundant extra-cellular mucus. Young metastases in the lungs showed prominent hysine caputes like those depicted by Cappell.

Case II (Reported b) Car) and Willir 1932 and 1933)—A man 36 years old at death had had symptoms of his sacral tumour for 5 years Necropyr showed the large gelatinous tumour to cocupy most of the pelvic cavity and to have destroyed most of the sacrum

or other tissues resembling chordoma, as was probably the case in the sacral tumour of a 7 months foctus described by Hennig (1900) Harvey and Dawson also expressed such doubts in the legends to their figures 34, 38, 39 and 40 However, that true chordoma does occur in children is shown by such cases as that reported by Ellis (1935)

The average age at which the patients first come under observation differs decidedly according to the site of the tumours—the mean ages of 20 cranial cases reviewed by Stewart and Morin was 35 years, and of 28 sacral cases 51 years. This seems to be a greater difference than can be accounted for by earlier onset of symptoms in the cranial cases

(3) Sex

The 220 cases reviewed by Harvey and Dawson comprised 144 males and 76 females. The preponderance of males is more marked in the sacral than in the crainal group. It has been suggested that trauma plays a part in the causation of chordoma, and that this may account for the different hability of the sexes, but this is very doubtful. (See Hueper, 1942).

(4) Co-existing anomalies

Several reported cases of chordoma showed other skeletal disease In Cappell's second case, a chordoma of the fourth cervicil vertebra was accompanied by an independent ecchordosis of the dorsim sellae, my Case I (above) had multiple exostoses of many bones and Harvey and Dawson mentioned a case of crainal chordoma associated with multiple chondromas of the left arm. These cases are insufficient to suggest more than a possibility that some constitutional tendency to skeletal anomalies may underlie the genesis of chordomas.

THE GROSS STRUCTURE OF CHORDOMAS

The typical chordoma is a slowly growing well defined lobulated tumour, consisting of soft gelatinous tissue, often with areas of haemorrhage, cystic degeneration or calcification, and sometimes with areas of more solid white tissue. It invades, distends and destroys the neighbouring bone, and extends into adjacent regions, the nasopharynx or orbits or the retropersioncal tissues or thigh. A huge size may be attained by the sacral tumours e.g. that recorded by Stewart and Morin had a circumference of 80 centimetres, the tumour of my Case I weighed about 200 ounces, and that of Graf's case 9 kilograms. The spheno occupital growths of course do not attain such large sizes, they usually project prominently into the crainal cavity, sometimes into the pharynx also, as in Case IV, and only rarely into the pharynx only

THE MICROSCOPICAL STRUCTURE OF CHORDOMAS

The microscopical appearance of chordoma is rather variable but in represensative pieces of tissue easy of recognition. The cells are usually aggregated in irregular groups, separated by stromal connective tissues or by the mucoid matrix of the tumour itself. They vary greatly in size and shape but in compact healthy regions of the growth fairly uniform polyhedral cells may be grouped to

of the first and second dorsal vertebrae and at operation by Mr Balcombe Quick a quantity of frable growth which was compressing the cord was removed. In August 1944 there was massive recurrence in the muscles of the back in spite of intensive λ ray irradiation. Microscopically the tumour was a chordorra



Fig 455 -Case II Typical chordoma (y 120)

SITE AGE AND SEX DISTRIBUTION OF CHORDOMAS

(1) Site

Harvey and Dawson's review of 240 cases of chordoma showed the following distribution

| Cranial - | - | - | - | - | 88 | (37 | per | eent) |
|--------------|-------|---|---|---|-----|-----|-----|-------|
| Vertebral | - | - | - | - | 30 | (12 | ** |) |
| Sacro-coccye | eal . | _ | _ | _ | 122 | (51 | | ì |

Horwitz's review of 245 eases gave the corresponding percentages as 33 $\,$ 12 and 55 $\,$

(2) Age

According to Harvey and Dawson the age distribution of 211 cases was

| Decades - | - | - | - | t | 2 | 3 | 4 | 5 | 6 | 7 ' | 8 | , 9 | _ |
|-------------|---|---|---|----|---|----|----|----|----|-----|---|-----|---|
| No of cases | - | - | - | t4 | 7 | 21 | 44 | 35 | 46 | 40 | 2 | 2 | _ |

Thus no age is exempt and there is no well-defined peak of distribution in any particular decade. There is room for doubting the correctness of the diagnosis in some of the incompletely investigated sacro-cocygeal tumours in infants, some of these may have been teratomatous with extensive areas of earliageinous

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resemble cords or clumps of epithelium The characteristic cytoplasmic and intercellular vacuolation, little in evidence in the smaller polyhedral cells, becomes prominent in the larger 'physaliphorous cells, in which cell outlines may be lost and the appearance may be that of a highly vacuolated syncytium Vacuolated cells may assume signet ring forms In areas of greatest mucus formation only scattered islets of cells remain in a sea of mucinous matrix. This extra-cellular material gives the usual staining reactions of mucin but the intra cellular vacuoles often appear empty or their contents fails to stain selectively. Intra cellular glyeogen, described by some writers, is difficult to demonstrate in most tumours Multinucleated cells are not uncommon and occasionally as in my Case I, they attain huge sizes and contain many nuclei. Mitotic figures are rare. Nuclear vacuolation has been described but is unusual. Grouping of flattened cells in whorls is a rare feature well depicted by Stewart and Morin. In some areas of compact growth the cells assume fusiform shapes presumably from compres sion Isolated clumps of tumour tissue sometimes develop a distinct hyaline sheath deliminating the tumour from the surrounding tissues and resembling the sheath of a young notochord (Cappell Willis, Harvey and Dawson) Some of these various features are depicted in Figs 454 and 455

THE METASTASIS OF CHORDOMAS

Chordoma, although an invasive almost always fatal growth does not often metastasize widely. Metastasizes in lymph glands were reported by Peters (1919) Lewis (1921) and Pototsching (1919) and Pototsching sease also had metastases in the liver. Stewart is case had large secondary growths in the soft tissues of the buttook and over the scapula but no visceral metastases were found at necropsy My Case I had widely disseminated blood borne metastases in many organs and Case II had small metastases in the liver only doubtless due to transport in the portal blood stream from the pelvis. Graf's ease had metastases in lymph glands liver lungs and skin.

PROGNOSIS AND DURATION OF CHORDOMA

The ultimate outlook of eases of chordoma is uniformly bad but many of the tumours are of slow growth and some of the patients survive for many years Stewart and Morin found the average duration of cranial cases from the onset of symptoms to be 28 years and of sacral cases 64 years. Even when complete removal of a growth appears to have been achieved prognosis must be guarded, in Stewart's case recurrence ensued after 5 years apparent freedom from disease following excision. The total duration in this case from first appearance of the tumour to the patient's death was 19 years

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Wells tabulated a number of records of certainly or probably congenital nephro biastomas. There exist reports of several specimens found in foctuses, e.g. Nicholson's (1931). All large series show a majority of cases with symptomatic onset in the first 3 years of life, and cases with onset after the age of 10 are very rare (Hedren, McCurdy, Herzog).

"Mixed tumours' have often been reported in adults but very few of these withstand critical examination. Thus the adult crises reported by Hedren (Case 3), Kilbane and Lester, Papin et al., Busser et al., Hamm, and Sparks can be dismissed, the tumours were probably carcinomas of ordinary adult type, with anaplastic



Fig. 456—Case I Nephrobiastoma Cellular tissue differentiating into both tubules and non epithelial tissue (× 100)

areas So also was the tumour reported by Moore in a man aged 56, in which the areas of bony tissue were probably the result of stromal metaplasia in a long standing carcinoma. Bosse rightly warned against mixtaking glomerulus like formations for true glomerulis in renal or other adenocarcinomas. Muss sthird case appears to have been a genuine one of mixed tumour in a woman aged 34. The tumour in Busse's second case, a large rhabdomyoma of the renal capsule in a woman aged 57 may have been related to the embryonic mixed tumour, though no epithelial elements were, found in it. In Hossholt's case also, a tumour from a youth aged 18 contained spindle celled growth and cartilage but no epithelium. In Hasner's third case in a man aged 45, while no histological details are given, the two good photographs certainly depict both tubules and striated muscle fibres. I have examined one undoubted specimen of embryonic renal tumour from a man aged 30, thoroughly studied by H. A. Sissons.

CHAPTER 60

EMBRYONIC TUMOURS OF KIDNEY AND LIVER AND GENERAL COMMENTS ON EMBRYONIC TUMOURS

We have already discussed several distinct kinds of truly embryonic tumours neuro-epithelioma and medulloblastoma of the brain neuroblastoma of the sympathetic system retinal neuro-epithelioma or retinoblastoma, and rhabdomyosarcomas of the pelvic organs and some other parts. Two other kinds of truly embryonic tumours remain for consideration, namely nephroblastoma or embryonic tumour of the kidney and hepatoblastoma or embryonic tumour of the liver. Some general comments on the significance of embryonic tumours will be added

EMBRYONIC TUMOURS OF THE LIDNEY NEPHROBLASTOMA

Many names have been applied to the embryonic renal tumours— adenosarcoma myo-sarcoma" mixed tumour, Wilms s tumour', 'embryoma, embryonic nephroma and nephroblastoma. These of course do not imply different kinds of tumours but merely structural variants or different notions regarding histogenesis. It is now clear that there is but one entity embryonic renal tumour, appropriately called also nephroblastoma' since it arises from and consists of immature renal blastema.

The earliest descriptions of these growths include those of Eberth (1872) Cohnheim (1875) Marchand (1878) Eve (1882) and Williams (1882) Eve however recorded a bilateral Hunterian specimen which must have dated from 1790 or earlier Good reports and reviews include those of Muus (1899) Hedren (1907) and Kretschmer and Hibbs (1931)

The following case provided a typical specimen

Case 1—Histon—A male child who had weighed 4 pounds when delivered by Cassarena section because of maternal renal disease developed normally until 15 months old when he began to suffer from haematuma and to pass small neces of flesh Microscopically these consisted of necrotic cellular tumour tissue—the right kidney was paipably enlarged and nephrectomy was performed. The child remained well? years later at the age of 81 Specimen—The kidney was largely replaced by a well-defined lobulated tumour 9 × 8 × 6 centimetres confined within the renal capsule and showing a compressed rim of kidney tissue at parts of the periphery. It consisted of homogeneous while tissue except for some haemorrhagic changes in polypoid masses of growth which filled and distended the calices and pelvis. Histological structure is shown in Figs 456-461 thiolica and pro-glomeruli in all stages of formation, much young connective tissue smooth much filled and on the control of the part of pelvic problems and perception and coassonal groups of strated muscle filters. The polypoid masses in the pelvis are clothed in most places by a layer of pelvic epithelium which dips down deeply into be intervening crypts of this part of the tumour.

(1) Age incidence

Most of these tumours are discovered in infancy or early childhood and there is no doubt that in a high proportion of cases they were already present at birth

(a) Invasion of veins

This is sometimes conspicuous, and is of course an important factor in prognosis. Examples of extensive growth within the renal veins and inferior vena cava and even into the heart are recorded by Merkel, Engelken, Muus, Rosen stein, Loughnane and Dew, in Dew's case, the left sided renal tumour extended to the cord and testis within the spermitte veins.

(b) Metastases

These are most frequent in the lungs but may occur also in liver, bones, lymph nodes and peritoneum. Noteworthy reports include those of Merkel, Engelken, Hedren (Case 5), Loughnane, Fraser, Wollstein, Kretschmer and Hibbs, Grewal, and Mintz, the last two writers particularly describing metastases in bones. In many cases the structure of the metastases has been as complex as that of the primary tumour, showing the immaturity and multipotentiality of the neoplastic blastema cells transported.

(6) Embryonic renal tumours in animals

Tumours undoubtedly comparable with the embryonic tumours of the human kidney occur in the pig (Feldman 1932 Chapter XXI), ox (Feldman Fig 188) sheep (Feldman, 1933), rabbit and hare (Bell and Henrici, Scott, Polson, Eisler), rat (Bullock and Curtis, Ratcliffe) and fowl (McKenney, Feldman and Olson) Nephroblastomas are the commonest of all tumours in pigs and are also relatively frequent in chickens Most of the affected animals are young As in humans, most of the tumours are unilateral and solitary, but bilateral growths sometimes occur, as in 8 of Feldman s 46 tumours of swine and in the fowl reported by Feldman and Olson In structure the growths generally resemble their human counterparts, showing a mixture of undifferentiated tissue and differentiating tubular, glomerular and connective tissues (Many excellent figures by Feldman) Conspicuous squamous change, as in Feldman and Olson's specimen is infrequent, and striated muscle fibres, as in one of Bullock and Curtis's rats, have rarely been seen Metastasis has been observed in the pig, or and sheep rarely in the fowl and not at all in the rodents, in which the rumours appear to be relatively benign

EMBRYONIC TUMOURS OF THE LIVER HEPATOBLASTOMA

Tumours clearly comparable with the embryonic tumours of the kidney occasionally arise in the liver. They occur in the foctus or young infant, and consist of embryonic liver tissue, sometimes accompanied by heterotopic tissues also. In considering these tumours three sources of confusion are to be avoided, namely (i) metastatic neuroblastoma must not be mistaken for a primary liver tumour, (ii) congenital angiomatosis must be distinguished from hepatoblastoma and (iii) primary carcinoma of adult type occurring in childhood or youth should be distinguished from embryonic hepatoma. For a good discussion of the several kinds of malignant hepatic tumours in infancy, consult Well's paper (1940). The tumour in a gril aged 9 reported by Kilfoy and Terry is a good example of a hepatic carcinoma probably not of embryonic origin, and the same applies to many of the other cales tabulated by them. It must be admitted,

(2) Sex incidence

In most series males are about twice as numerous as females (Kretschmer and Hibbs, McCurdy Herzog)

(3) Site

The tumours are usually single and unilateral, but multiple or bilateral growths occur as in Eberth's Cohnheim's and Merkel's eases the Hunterian specimen referred to by Eve Hedren's first case, 2 of the 17 eases reported by Kretschmer and Hibbs and in 8 of the 107 eases reviewed by Herzog Hedrén's ease was remarkable in showing 2 separate tumours in the right kidney 3 in the left and also microscopie foci of undifferentiated tissue in other parts of the kidneys



Fig. 457—Case I. Nephroblastoma theomphatety differentiated epithelial clumps in mesenchyme like connective tissue (\times 100)

(4) Structure and histogenesis

The structure varies greatly. In most tumours embryonic renal tissue showing different degrees of differentiation predominates, while various hetero topic tissues may also appear in varying proportions. (See Figs. 456-461.)

(a) Undifferentiated tissue

This is often plentiful and constitutes the bulk or even the whole of some tumours. It resembles and undoubtedly corresponds to early embryonic renal blustema. All stages in the transformation of this tissue into differentiated renal or heterotopic tissues can be traced.

(b) Fpithchal structures

These show great diversity of form including undifferentiated epithelial

(a) Invasion of veins

This is sometimes conspicuous, and is of course an important factor in prognosis. Examples of extensive growth within the renal veins and inferior vena cava and even into the heart are recorded by Merkel, Engelken, Muus Rosen stein, Loughnane and Dew, in Dew's case, the left sided renal tumour extended to the cord and testis within the soermatic veins.

(b) Metastases

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however, that distinction between truly embryonic liver cell tumours and ordinary hepatomas arising in childhood may be neither histologically, possible not theoretically valid, they may differ only in their time of origin. In view of this, it would be pointless to attempt analysis of the age incidence and other properties of hepatoblastomas. Suffice it to recognize that there are tumours of liver tissue of unquestionable embryonic qualities. It will be helpful to review briefly a few typical examples

(1) Some examples of embryonic hepatic tumours

Nissel described a large turnour of the liver of a new born infant, con sisting of epithelial tissue of trabecular arrangement accompanied by much spindle-celled mesenchymal tissue containing areas of cartilage and bone. Nissel supposed the turnour to have arisen from a focus of embryonic liver tissue con taining both epithelium and connective tissue and the bone and eartilage to have developed from the latter by metaplasia.

In Sheehan's case, a large tumour of the right lobe in a firl aged 6 years was associated with congenital cystic disease of the organ, and the tumour had massively invaded the common bile duct and had produced several discrete metastases in the liver itself. Microscopical examination showed the cystic bile ducts to contain papillary growths, and the tumour to consist mainly of nonepithelial tissues derived from the abnormal connective tissue of these papillary These were myxomatous fibromatous and rhabdomyomatous, but with all transitional forms. Early papillary growths in the cysts showed mesenchymal changes similar to those in the main tumour, including the develop ment of mucoid tissue and of striated fibres. Sheehan's views regarding the histogenesis of the tumour are worth citing In view of the tissue balance during early foctal life between the hypoblastic liver bud and the mesen chyme into which it grows we may expect a maldevelopment of the one to lead to a reciprocal maldevelopment of the other. The later supervention of active growth on the part of the hypoblastic cells will then lead to the formation of eareinoma or hepatoma, and on the part of the mesenchymal cells to sarcoma of various kinds The participation of both divisions leads to the true mixed In the present case the hypoblast has not developed to hepatoma and remains benign as the epithelium of the cysts while the embryonic connective tissue cells have undergone the malignant development

In a female infant II months old with marked overgrowth of the left side of the body, Roth found a large hepatic tumour composed of hepatoma like epithelial growth, foci of cornifying squamous epithelium and young mesen chymil tissue containing patches of cartilage and hone

Webster described three specimens of malignant hepatoma from male infants aged 6.4 and 18 months. The first tumour contained much carcinomatous ussue of diverse arrangement but resembling hepatic tissue, much osteoid tissue with patchy calcification, and sarcomy like areas of cellular connective tissue and Webster regarded it as an hepatic analogue of Wilms's tumour. The tumours in Webster's second and third cases consisted of hepatoma like epithelial growth only, and showed no noteworthy stromal changes.

In the following personally studied case also the tumour was a simple embry onic hepatoma without any heterotopie tissues

(a) Invasion of veins

This is sometimes conspicuous, and is of course in important factor in prognosis. Examples of extensive growth within the renal veins and inferior vena cava and even into the heart are recorded by Merkel, Engelken. Muus, Rosen stein, Loughnane and Dew. in Dew's case, the left sided renal tumour extended to the cord and testis within the spermitte veins.

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In a female infant II months old with marked overgrowth of the left side of the body. Roth found a large hepate tumour composed of hepatoma like epithelial growth, foci of cornifying squamous epithelium and young mesen chymal tissue containing patches of cartilace and bone.

Webster desembed three specimens of malignant hepatoma from male infants aged 6 4 and 18 months. The first tumour contained much careinomatous tissue of diverse arrangement but resembling hepatic tissue much osteoid tissue with patchy caleification and sareoma like areas of cellular connective tissue and Webster regarded it as an hepatic analogue of Wilms's tumour. The tumours in Webster's second and third cases consisted of hepatoma like epithelial growth only and showed no noteworthy stromal changes.

In the following personally studied case also the tumour was a simple embry once hepitoma without any heterotopie tissues

and young children (e.g. many of the congenital sarcomas tabulated by Wells) are of this nature, that is, they have arisen from and continue to reproduce undifferentiated mescendyme, they are embryonic mesenchymomas. Since adult mesenchymal tissues may contain plastic indifferent cells or may revert to embryonic condition when they multiply (see Chapter 41), sharp distinction between primarily embryonic mesenchymomas on the one hand and mesenchymomas with reversionary embryonic qualities in adults on the other, is probably impossible. Yet, for theoretical reasons set forth in the following paragraphs, we should attempt to make the distinction as far as nossible

GENERAL COMMENTS ON THE CAUSATION AND SIGNIFICANCE OF EMBRYONIC TUMOURS

Most of the ordinary tumours of adult life arise only after prolonged exposure of the tissues to carcinogenic chemical substances or other agents. This cannot apply to embryonic tumours they arise during actual organogenesis from tissues still immature and some of them attain large sizes and produce metastases even during the brief span of intra uterine life. The causes of these growths must be very different from those of adult tumours, they must be sought in disturbed embryonic chemistry—life chemistry of the organisers, those substances which are responsible for the mutual inductive effects of one tissue on another during organogenesis and differentiation. Yet, when discovered, the chemistry of these disturbances may well shed light on the fundamental problem of tumour growth, the very nature of the irreversible change in the tumour cells. For this reason, the embryonic tumours and the kindred teratomas are of peculiar interest and ment the closest study.

The embryonic tumours are simultaneously tumours and malformations In Chapter 1 it was pointed out that not all malformations are congenital, but that errors of development may and do arise during post-natal life, in tissues which are still immature, such as the bones teeth and gonads. This applies also to the embryonic tumours, theoretically the time range of possible origin of an embryonic tumour of a particular kind is the whole period-post natal as well as foetal-during which the parent tissue remains immature and we should expect tumours originating early in the embryonic or foetal period to be less mature and more malignant than those arising later. The age incidence of the several kinds of embryonic tumours accords well with this theoretical concept Thus immature neuroblastic tissue is scanty in the sympathetic system soon after birth most neuroblastomas make their clinical appearance within the first 3 or 4 years of life, and the earliest appearing are on the average the most em bryonic Retinal differentiation is complete at or soon after birth two thirds of retinoblastomas have become clinically apparent before the age of 3 Cerebellar differentiation is nearly complete by the end of the first year of post natal life, but some proliferation continues at the rhombic lip much later than this cerebellar medulloblastomas arise chiefly in young children but occur also in older children and adolescents Formation of renal tissue from the immature nephrogenic cap is complete soon after birth the majority of nephroblastomas are discovered before the age of 3 years. We cannot put a terminal date to the formation of new liver tissue for this tissue has great powers of regeneration

however, that distinction between truly embryonic liver-cell tumours and ordinary hepatomas arising on childhood may be neither histologically, possible nor theoretically valid they may differ only in their time of origin. In view of this, it would be pointlest to attempt analysis of the age incidence and other properties of hepatoblastom's Suffice it to recognize that there are tumours of liver tissue of unquestionable embryonic qualities It will be helpful to review briefly a few typical exampler

(1) Some examples of embryonic hepatic tumours

Nissel described a large tumour of the liser of a new born infant, con sisting of epithelial tissue of trabecular arrangement accompanied by much spindle celled mesenchymal tissue containing areas of cartilage and bone. Nissel supposed the tumour to have arisen from a focus of embryonic liver tissue con taining both epithelium and connective tissue and the bone and eartilage to have developed from the latter by metaplasia

In Sheehan's case a large tumour of the right lobe in a girl aged 6 years was associated with congenital cystic becase of the organ and the tumour had massively invaded the common bill duct and had produced several discrete metastases in the liver itself. Micoscopical examination showed the evision bile duets to contain papillary growths and the tumour to consist mainly of non enthelial tissues derived from the abnormal connective tissue of these papillary formations These were myxomatous Spromatous and rhabdomyomatous but with all transitional forms. Early popullary growths in the cysts showed mesenehymal changes similar to those in the main tumour, including the develop meet of mucoid tissue and of strated fibrs. Shechan's views regarding the histogenesis of the tumour are worth eating. In view of the tissue balance during early foetal life between the hypotastic liver bud and the mesen chyme into which it grows, we may expect maldevelopment of the one to lead to a reciprocal maldevelopment of the other. The later supervention of active growth on the part of the hypoblastic collection in the lead to the formation of carcinoma or hepatoma and on the part of the mesenchymal cells to sarcoma of various kinds. The participation of both traisions leads to the true mixed In the present case the hypoblast as not developed to hepatoma and remains benign as the epithelium of the combine while the embryonic connective tissue cells have undergone the malignant development

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onic hepatoma without any heterotopic tissues

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even in the adult, but most of the clearly embryonic hepatic tumours especially those with heterotopic elements, have been found in young infants. Again as already pointed out the great powers of adult mesenchymal tissue for proliferation and aberrant redifferentiation make it difficult and perhaps unnecessary to distinguish sharply between embryonic mesenchymal tumours and those developing later.

What of certain other tissues the adult differentiation of which is not complete until long after birth especially the skeleton and teeth? Can embryonic tumours arise post natally in these? In a sense yes. The properties of multiple exostoses, ossifying ecchondromas and hereditary enchondromas, the causes of which are clearly related to developmental disturbances are in part determined by their having arisen from young growing skeletal tissues. Perhaps the causes of some of the osteogenic sarcomas and osteoclastomas of children and adolescents are to be sought more in disturbances of the chemistry of skeletal growth than in the direct application of extrinsic carcinogenic agents. Of course succomas of bone can be produced by radio active substances or by the experimental insertion of hydrocarbons but these causes may be false guides to knowledge of the causation of most of the bone tumours of youth for which greater understanding of calcium and phosphorus exchanges and of the enzymes and metabolism of young bone tissue may be much more relevant. Tooth tissue is immature throughout childhood and early adolescence, and it is significant that in the majority of eases tumours of the paradental residues the adamantinomas adolescence or early adult life. It seems unlikely that these residues can be subjected to extrinsic carcinogens and much more probable that the causes of neoplasia in them may be disturbances in their own metabolism and growth during their formation. In this sense the adamantinomas of the iaw may be looked upon 1º embryonic tumours, 1e as tumours arising in a still immature tissue and evoked by factors disturbing the growth and maturation of the tissue The same applies to the adamantinomas of the parapituitary residues which also arise during childhood in a high proportion of cases

The great significance of the embryonic tumours is that they show that carcino genesis does not always imply the application of identifiable carcinogenic substances from without but may result also from disturbances of metabolism and maturation of growing tissues. Of course these disturbances are themselves caused no doubt by external factors genic in the ordinary sense. They may merely consist in certain combinations of circumstances—excess or defect of particular mineral or nutritive substances vitamins hormones oxygen etc—which so impede or deviate normal growth and differentiation that neoplasar results. It is possible that the disturbed metabolism itself results in the formation in the developing tissues of carcinogenic chemical substances perhaps of a sterol nature which might be extracted and identified. All this of course is speculative but we are constrained to such speculations by the peculiar phenomenon of embryonic neoplasia, which clearly demands very different concepts regarding eausation from those which occupational and experimental studies have engendered.

CHAPTER 61

THE TERATOMATA

INTRODUCTION

"FAR from adopting the time honoured method of human teratology of taking the lightest fancies of our predecessors for gospel (provided they have acquired substance and reality in print), we must lay down rules for our guidance. adhere to them rigidly and ruthlessly refuse to entertain all nonconforming utterances of authority. And we cannot do better than allow ourselves to be guided by the Cartesian axiom, that we are not bound to accept—indeed, that we are properly bound not to accept—a proposition that is not perfectly clear and distinct (Nicholson, 1935 Study No XVI, p 10)

In view of the arresting heterotopic structures seen in many teratomas, it is not surprising that study of these growths more than any other group of tumours has been confused by fanciful hypotheses. False identification of bones, organs and whole parts of the human body without proper dissection or microscopical study, has abounded and at least a dozen different histogenetic hypotheses, based on no more than their authors imaginations have been advanced and endlessly debated. Some of the main hypotheses will be discussed at the end of this chapter after the structure and behaviour of the tumours have been described

It would be a useless task to attempt a critical outline of even the chief of the huge number of papers on teratomas Amongst the best reviewers of those of last century are Ahlfeld (1875), Wilms (1896) Askanazy (1907) and Ohkubo (1908) Of the more recent contributors to the subject by far the most important for his critical scientific approach is Nicholson (1929, 1930 1934 1935 and 1937), whose thoroughness of description I have tried to emulate in my own studies (1935 1936 and 1937)

DEFINITION AND CLASSIFICATION

(1) Definition

A teratoma is a true tumour or neoplasm composed of multiple tissues of

kinds foreign to the part in which it arises

It is a true tumour 10 it displays some degree of progressive uncoordinated growth and is not merely a quiescent malformation. Teratologists have often confused teratomas and malformations devoid of neoplastic qualities. It is true that some highly differentiated teratomas, e.s. some of the so-called "dermoid cysts", come to consist of quiescent tissues of mature adult type but this applies to some individual members of almost any group of tumours Some 'dermoid cysts' though the most benign members of the teratoma family, display progres sive growth and these cannot be sharply separated from polycystic and solid teratomas of more active growth less complete maturation of the tissues, and potential or actual malignancy Non neoplastic malformations lack these

EMBRYONIC HEPATIC TUMOURS kilfoy E J and Terry M C (1929) Surg Gyn Obst, 48 751 Nissel W (1928) Firchous Arch, 269 446 Roth F (1938) Firnkfurt Z Path 52 163 Shechan H L. (1930) J Path Bact 33 251 Webster R (1938) Med J Austral in 381

Even a mixed tumour arising during early stages of development is not a teratoma if it contains only regionally indigenous tissues, e.g. the compound salivary glandular and lipomatous tumour of Case I. Chapter 42 So also, we should distinguish between teratomas and embryonic tumours of particular viscera such as nephroblastoma and hepatoblastoma, even though some of the latter are "mixed tumours in that they show aberrant differentiation of some of their embryonic tissues Thus Wilms's tumours' of the kidney, even though they may contain striated muscle fibres cartilage or squamous enithelium, are still clearly nephroblastomas derived from and composed of embryonic renal tissue heterotopic tissues in these tumours display the dormant potencies for aberrant differentiation inherent in embryonic renal tissue, comparable with the metaplastic potencies of adult tissues but the tumours do not produce completely exotic tissues, such as salivary, respiratory, dental or neural tissues, all of which are common in true teratomas. However, in common with teratomas, the mixed embryonic tumours of particular organs have their origins in developmental disturbances at early stages and a capacity greater than that of matured tissues for diverse differentiation. They differ from teratomas in their more restricted potencies, a restriction clearly related to the regional restriction of potencies within the particular organs or localities from which they arise

(2) Classification

All teratomas constitute a single class and sub divisions of the class on either structural or behaviouristic grounds are arbitrary. This principle has been repeatedly enunciated by almost all serious students of the subject including Wilms, Askanazy, Ohkubo, Nicholson and myself.

Structural sub division into cystic and solid growths into monodermal bidermal and tridermal ones, according to the number of 'germ layers' repre sented by the tissues discovered in them, and into those composed of mature adult tissues and those containing embryonic tissue, are all quite artificial Pre dominantly cysic growths contain plenty of solid tissues, predominantly solid growths almost always contain plentiful small cysts. The number of tissues discovered and whether these represent derivatives of one, two or three of the germ layers of normal ontogeny depend mainly on how thorough the search has been full examination will show that almost all teratomas are "tridermal" for they almost all contain skin teeth or nervous tissue (' ectoderm '), respiratory or alimentary epithelia ('endoderm'), and they all contain connective and vascular tissue at least ('mesoderm') But, in any case, the three germ layers of normal development have no real relevance in the structure of teratomas for these show no evidence whatever of orderly delamination Division of teratomas into those composed wholly of mature tissues and those containing embryonic tissues is of practical value, for the former are usually benign and the latter malignant, yet the distinction is arbitrary, since all degrees of maturity of the tissues are encountered and since mixtures of adult and embryonic tissues in all proportions occur

The behaviouristic distinction between "beingin and "malignant tera can be made in most cases. But, as with other classes of tumours, be and malignant are relative terms, and borderline tumours occur. Str.

teratomas benign Structure qualities Masses of pancreatic and gastric tissue in the walls of Meckel's divert scula, branchial cysts, enterocysts, developmental dermoid cysts beneath the skin of in the cranial cavity or spinal canal—all of these are malformations con taining multiple heterotopic tissues, but they are not teratomas, nor related to them Also to be distinguished from teratomas are double monsters, acardiae amorphous and other forms of suppressed twins, whether externally attached or included (if this ever happens) and duplications of main parts, these also lack neoplastic attributes. It is I believe, a mistake to suppose that a gentle series of gradations exists between double monsters and malformed twins on the one hand and teratomas on the other-a mistake widely promulgated because of a prevalent view that teratomas are included monsters or malformed twins The sooner this misconception is abandoned the better. There may be occasional specimens the nature of which it is difficult to decide whether teratomatous or monstrous formations e.g. some of the epignathi. But I personally have yet to see such a specimen none of the many teratomas and malformations which I have examined properly has occasioned any such difficulty. Moreover, the descriptions of many of the supposed examples of borderline or transitional lesions between teratomas and monsters show how incompletely the specimens were examined

Teratomas contain multiple tissues. The more thoroughly they are examined. the greater the variety of tissues found in them. The notion that some of them contain only one kind of tissue or tissues of only one germ layer' is almost always a confession of inadequate examination. Even in the simplest 'dermoid evsts, proper topographical study will rarely fail to reveal in addition to skin and its appendages and adipose tissue other kinds of tissues also-neural skeletal dental respiratory or alimentary. This is the place to insist-what indeed should be self evident-that a teratoma has not been adequately studied until it has been thoroughly dissected and all relevant structures examined micro sconically or until it has been topographically reconstructed from serial sections in the ease of small tumours or, in the case of large tumours from thin serial slabs, as described in my papers. The only teratomas which consist of only one kind of tissue are those rare highly malignant growths composed of completely undifferentiated embryonic tissue the differential potencies of which are of course not manifested as in the recurrent growth in the ease providing my specimens Nos VIII and XIX (1937) How unwise it is to regard as teratomatous' tumours devoid of demonstrably multiple tissues is seen in Ewing's hypothesis of the nature of seminomas this has been dealt with in Chapter 33

Teratom's contain tissues of kinds foreign to the part. There are many mal formations and some tumours composed of and derived from multiple tissues indigenous to the region but these are not teratomas. A mammary, fibro adenoma though composed of two distinct neoplastic tissues is not a teratoma because these tissues are both mammary tissues. It is not even a teratoma when its fibroblastic component undergoes cartiligenous and bony changes, for these are but metaplasias often displayed by fibroblastic tissues under abnormal conditions. So also mixed tumours of the adult thyroid uterus or other parts should be distinguished from teratomas because their tissues represent and are derived from those of the region even though they may assume metaplastic disguises.

(1) Teratomas of the ovaries

(a) Type

These the most familiar of all teratomas need no detailed description, many typical examples are given in the papers already eited. Most of them are of the benign highly differentiated, cystic variety—so-called 'dermoid cysts' (Figs 464 465). This term however, is unfortunate for two reasons—(a) the same name is applied (and correctly so) to lesions unrelated to teritomas, the sequestration dermoid cysts of the skin cranial cavity and other parts, and (b) to call any teratoma a dermoid cyst' is to give always an incomplete and often an erroneous

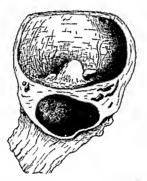


Fig. 464—Drawing of benigh teratoma of overy containing two large and several small cysts with a skin-covered eminence carrying a tooth in the largest cavity. The divided mesovarium is below. (Billis 1935 Case FY) (Natural size)

in a dermoid cyst one or more of these cavitus has become distended by accumulating sebum to form the bulkiest part of the growth, the other components of which now form a relatively small solid or cystic eminence projecting into the sebum filled cavity. This eminence always contains tissues other than skin of as great a variety as those seen in the solid and polycystic teratomas. Frequently, too the main cavity is lined partly by skin and partly by other tissues, respiratory, alimentary or nervous and it contains not only sebum but also mucus and other secretions of these tissues. In some tumours the main cavity is lined entirely by one of these tissues and not at all by skin, e.g. in my Case XXI (1937) it was lined by nervous tissue and choroid plecus and its contents was clear fluid undoubtedly ecrebrospinal fluid. In a small minority of cases ovariant teratomas are solid and malignant as in my Case XV (1937) and Webster's case (1938)

is usually, but not always a safe guide in prognosis, e.g. the bilateral tumours VXVIII and XIX of my 1937 paper had a well differentiated beingn" structure yet highly malignant recurrent growth rapidly developed while tumour XVII contained active tissues of doubtful maturity and innocence but the patient remained well several years after removal of the growth. However tumours which contain clearly embryonic components are usually elinically malignant

THE SITES OF TERATOMAS

The main sites of teratomas are in order of frequency, the ovaries the testes, reterportoneal region the anterior mediastnum, pre sacral and coocygeal region and the base of the skull. Rarer sites include the pineal gland brain and neck Teratomas rarely, if ever, arise in the face posterior mediastnum thoracic and abdominal viscera (other than the gonads) thoracic and abdominal walls and the extremites. The few teratomas' which have been reported in these situations are of dubious nature, some at least of them have certainly been imperfect twin inclusions or other non neoplastic malformations while others have been non teratomatous mixed tumours (see breast, thyroid uierus bladder)

The following table shows the number and situations of the teratomas in 82 cases which I have studied, and gives references to the 42 cases reported

| Site | No of cases | Remarks | References to reports (a) Willis 1935 (b) 1936 (c) 1937 (d) 1939 (c) Stewart Willis and De Saram 1939 (f) Willis 1942 | | | |
|---------------------|-------------|---|--|--|--|--|
| Ovary | 50 | Benign 42 cases benign but with supercening carenoma 5 cases malignant teratoma 3 cases (Bilateral tumours in 6 cases) | | | | |
| Testis | 19 | All malignant (Associated with seminoma in 4 cases) | (a) Willis 1935 6 cases (b) Chapter 33 Cases 111-VI | | | |
| Epididymis | 2 | Both benign (Associated with seminoma in t case) | (a) Case I below (b) Chapter 33 Case VII | | | |
| Retroperatoneal - | 3 | All benign | (a) Willis 1935 (b) Gale and Willis 1944 | | | |
| Presacrat | 2 | Both benign | Willis 1935 (1 case) | | | |
| Arterior mediastina | 3 | All benign | Willis 1935 (2 cases) | | | |
| Intra pencardial - | 1 | Benign | Willis 1946 | | | |
| Brain - | . 2 | Both malignant | Cases II and III below | | | |

(c) Age

The mean age of 48 cases in my series was 33 years, the three voungest patients were 8 11, and 12, the largest number of cases (18) were in the third decade, 26 (i.e. more than one half), were under 30, the three oldest patients were 68, 67 and 63 and all three of these had carcinomas supervening in previously benign cystic teratomas (Cases IV VI and VII below) Two other patients (Cases V and VIII below) who also had supervening carcinomas, were 1ged 48 and 40

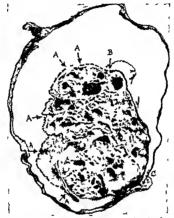


FIG. 466—Slice of an ovarian teratoria composed of a solid and polycystic mass projecting into a large thin walled cyst. Microscopically this mass was clothed by nervous tissue (continuous line) epidermis (interrupted line) and respiratory epithelium (dotted line) with abrupt transitions at A B and C (see Fig. 484). (Willis, 1937, No. YVII). (Natural size)

In sharp contrast with these cases of supervening malignancy of single tissues practically all of the malignant solid or polycystic teratomas occur in childhood or adolescence. Huge dermoidcysts' (see belon) arealways from middle aged or old subjects. Since most ovarian teratomas are obviously old tumours when they are first discovered—usually either because of their size or because of torsion or other complications—it is clear that these growths begin in very early life. Doran gave references to some of the first recorded cases of surgical removal of ovarian teratomas in young children of ages I year and 8 months 2 years, 2 years and 11 months and of 4.7 and 8 years, Shattock described a large tumour from a child aged 24 and Wakeley (1933) reported cases 8, 9 and 9 years of age

(d) Familial incidence

This has only occasionally been noted and is probably no more than fortuitous

A tumour of borderline type with a large solid or polycystic mass of well differ entiated but not fully mature tissues projecting into the main cyst is depicted in Fig 466

(b) Site

It has often been noted that ovarian teratomas occur with greater frequency in the right than in the left ovary and this also has been my experience. Of 50 cases which I have studied 20 had right sided tumours 8 left sided in 16 the side was not stated and 6 had bilateral tumours. In 7 of 31 cases studied by Doran (1884) the tumours were bilateral. Although it is quite possible that multiple separate teratomas may sometimes develop in one ovary proof of multiplicity

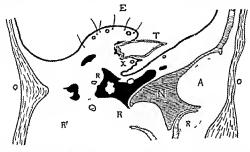


Fig. 46.5—Diagram of tissues found in vertical section of tumour shown in Fig. 46.4 Heavy black line is skin with hairs and glands. T = tooth X = position of paradental residues N = central nervous tissue. R = cysts lined by respiratory epithelium. A = cyst lined by alimentary epithelium. Black areas bone, close stupple cardiage—wide stupple adipose and connective tissue. O = byter of ovariant tissue. (× 2)

in so small an organ is difficult to obtain. The supposedly multiple teratomas described and reviewed by Norak may equally well have been merely multiple eysts of single teratomas. Aschheim described a case of bilateral ovarian teratomas accompanied by a separate intra tubal teratoma.

It is necessary to mention here in order to dismiss the claim of several workers to have seen the origin of a teratoma from the lining of an ovarian follicle. Thus, Thorition (1874) sink a teratoma associated with some supposedly simple Graafian cysts one of which contained a patch of hairy skin but there is nothing in Thorition's account to show that these simple cysts were not parts of the teratoma. Gradner (1938) saw a small teratoma in what he supposed to be an attetic follicle lined by granulosi cells but his description and figures suggest that his granulosi cells may well have been altered stratified epithelium lining a teratomatous exist.

(2) Teratomas of the testes

(a) Type

Most teratomas of the testis are solid malignant growths when first discovered, benign cystic growths form a small minority. Save for this reversal of the relative frequency of benign and malignant growths, the testicular tumours are in general smillar to their ovarian counterparts, and, as in the ovary, some tumours show mixtures of well differentiated tissues and malignant embryonic ones

(b) Site

Most series show a predominance of right sided growths, e.g. 43 right-sided to 23 left sided in Ohkubo's review 11 to 5 in my series. With rare exceptions teratomas of the male reproductive organs are intra testicular, teratomas of the epididymis are very rare. A formerly prevalent view, promulgated by Bland Sutton, that the usual origin of testicular teratomas was from the "paradidymis was certainly erroneous." Teratomas of the epididymis are exemplified in Case VII of Chapter 33 and in the following case.

Case I — A man aged 28 had an inguinal herina and had also noticed for 5 years a firm mass attached to the descended but small testis on the same side. Mr. A. F. Maclure of Melbourne repaired the herina and removed the testis with the attached tumour which was entirely extra testicular and occupied the upper part of the epidolymis. The tumour was a well defined mass 2 centimetres in main diameter containing multiple exist Microscopically it was found to contain cavities hined by chilated pseudo stratified epithelium columnar gobbic celled epithelium, or simple columnar or cubodial epithelium associated with plands resembling Brunner's glands a five small islands of panieratic tissue much smooth must, each occasional for of cartilize

Bilateral teratomas are rare but it is possible that a patient who has been found to have a teratoma in one testis is more likely than a normal man to have one in the other testis, though this enhanced risk has not been proved conclusively as it has for seminomia (see Chapter 33). There is, however, no doubt that the imperfectly descended testis is more liable than the normal organ to teratoma, as it is to seminoma, and that this applies also to the intra abdominal testes of pseudo hermaphrodites (Carmichael and Oldfield). It has been suggested by several workers that some retroperitoneal teratomas may arise from supernumerary testes which have occasionally been found in this region (Staemmler)

(c) Age

As already noted in Chapter 33, the mean age of patients with teratomas of the testis is about 30. The benign cystic growths are discovered in much younger patients than the commoner malignant ones most of them being found in children and some of them being noticed at birth. Wilms reviewed the older records and concluded that nearly all "dermoids of the testis were probably congenital of 31 cystic teratomas reviewed by Ohkubo 25 were discovered before the age of 25 and 16 before the age of 8 Examples of benign teratomas tound in infancy, and certainly or probably congenital include those of Genitz Parker Muller, Horst and Aboukhalil and Wakeley

Koltonski saw a mother and daughter both with ovarian teratomas, and Sippel three sisters

(e) Associated ovarian lesions

The association of ovarian cysts or cystadenomas with teratomas as described by Doran Stewart and Eglington and many others is probably only fortuitous since the former are very common and the latter far from rare. In only 5 of my 50 cases of teratoma were there associated ovarian lesions, these were simple cysts in 3 cases, pseudomucinous cystadenoma in 1 case and surface fibro papillary growths in 1 case all 5 patients were adults. Terationatous cysts lined by epithelium of intestinal type have probably been mistaken for pseudomucinous ovarian cysts. Except for a superficial resemblance there is no evidence to support a view at one time popular and still supported by Novak, that pseudomucinous cysts consist of teratomatous intestinal tissue. McCrea described a teratoma possibly of ovarian origin in a male hermaphrodite aged 31

(f) Size and contents

Huge sizes may be attained usually by the accumulation of sebum in benigh cystic growths. The contents of huge cysts sometimes form a multitude of spherical firm butter balls, doubtless from mechanical agirtion. Thomton (1876) described a patient aged 59 from whom 86 pints of sebaceous fluid were removed by tapping and from whom a similar amount had been removed 9 years earlier. Bland Sutton (1922) in his Fig. 298 depicted a dermoid eyst containing 3 930 sebum balls. The two largest tumours in my series were. (i) a unilocular dermoid lined by skin weighing 84 pounds of which 74 pounds consisted of sebaceous contents removed surgically from a woman aged 55 and (ii) a bilocular dermoid removed surgically from a woman aged 57 lined by skin and con taming teeth and 2 gallons of sebaceous fluid in which were suspended 1 800 butter balls, each about 15 centimetres in drimeter and a few larger hair balls.

(g) Secondary changes

Secondary changes of clinical importance in teratomas include torsion, rupture into the peritoneal cavity perforation or extension into rectum vagina or bladder infection and detachment from the ovary and implantation in other parts of the ab dominal cavity (Doran Lexer Williams Mayer Ottow James Schauberger) It is significant that as Williams pointed out practically all cases reported as having intra pelvie or rectal teratomas or dermoids have been females. Port s was " probably the earliest English account (1880) of a rectal dermoid removed from a girl aged 16 An early account of an unusually mobile ovarian dermoid with a long pedicle was that of Griffiths (1877) the tumour was first noticed at the age of 4 and was removed 8 years later A clinically unimportant but frequent change in cystic teratomas is desquamation of parts of the lining epithelium and the formation of reactive tissue with many phagocytic foam cells and giant cells as described by Stewart. Patchy cylicification of the degenerated will may ensue Thomson saw asthmatic reaction in teratomatous bronchial tissues nomatous change in benign cystic teratomas has already been referred to and is described later

described a retroperatoneal teratoma which extended laterally and posteriorly deep to the spinal muscles and caused a swelling in the back. Retroperatoreal teratomas of the lower lumbar or the pelvic region, like my Case XI (1935), are very rare

(c) Age

The early age of appearance of most retroperitoneal teratomas is exemplified by the following cases in Hosmer's case and in my Case X (1935), abdominal swelling had been noticed at birth in Nicholson's case the large tumour came from in infant 4 months old, in my Case XI (1935) the huge tumour (Fig. 467) was removed at the age of 9 months. Schonholzer's and Penberthy and Brownson's patients were 2 years old in Lexer's case a girl aged 11 was known to have had a large tumour for several years, in the case reported by Gale and myself the large tumour, consisting of fully mature quiescent issues and with every sign of being coeval with the patient, was discovered during routine examination of a girl aged 13, and Fuller and Jagger's patient, aged 19, also had a large 'adult' tumour clearly of long standing. These findings point clearly to the congenital nature of this group of teratomas.

(d) Sex

Females appear to outnumber males, e.g. the cases just cited comprise 7 females and 3 males

(4) Mediastinal teratomas

(a) Type

With few exceptions these are of the benigh cystic variety. Reports of malignant tumours include those of Virchow (1871) Ritchie Ceelen, Jacobs, Kantrowitz, and Houghton who reviewed records of 25 malignant tumours. The malignancy has usually been interpreted as adenocarcinomatous of 'chorion epitheliomatous change but in some cases it is total, yielding complex metastases, as in Houghton's case

(b) Site

Hedblom's useful review of nearly 200 cases showed that, almost without exception, intra thoracic teratomas occupy the anterior mediastimum. Recently (1946) I reported a case and reviewed 4 others in which the tumours were closely connected with the great vessels at the base of the heart and projected into the peticatifial cavity (Fig. 468). Posterior mediastinal teratomis are almost unknown

(c) Age

These growths have been discovered at all periods of life from infancy to old age. However in more than two thirds of the cases reviewed by Hedblom the patients were less than 30 years old. The malignant tumours mentioned above were from men aged 23, 24 33, 27 22 and 22 respectively and the mean age of

(d) Associated testicular lesions

Incomplete descent and pseudo hermaphroditism have already been referred to, and in Chapter 33 the association of teratoma and seminoma is discussed

(3) Retroperstoneal, mesenteric and mesocolic teratomas

(a) Type

Most teratomas in these situations are benign eystic growths which attract attention in childhood by their size or pressure effects (Figs. 467-475 and 477-479). Other tumours are solid malignant growths sometimes of chorion-epithelio matous" type these usually manifest themselves in early adult life. As Prym (1925 and 1927) insisted, eare must be taken not to mistake retroperitoneal



Fix 467—Diagram of structure of a since of large retropersioneal teratoma from a female infant 9 months old Central nervous sixue hashed choroid plessus existines marked C alimentary and respiratory cavities and glands finely stuppled and marked A and R skin cavities stippled and marked S bore and cartifage black and main masses of bone marked B X ≈ main cyst cavity (which contained 40 ounces of clear fluid)—wide supple denotes adoptive tixtue (B illu 1935 Case VI) (Slightly reduced)

metastases of small testicular teratomas for primary growths—and no malignant retroperatoriest tumour should be accepted as primary until the testes have been thoroughly examined. But cases like those of Fenster show that primary malignant retroperatoriest teratomas, unassociated with testicular disease—do occur

(b) Site

Most of the tumours arise high up in the retroperstoneal region close to the superior mesenteric artery coefuse artery panereas and kidneys. A tumour described by Nicholson (1929) was intumitely intached to the upper pole of the left kidney and derived its blood supply from the left renal and upper tumbar arteries. The tumour which Gale and I reported (Figs. 477–479) lay high up behind the panereas. Some tumours arising at the samelevel extend forward to occupy the root of the mesentery or mesocolon (Lever. Schönholzer) or even to be in the distal parts of the mesentery (Penberthy and Brownson). Fuller and Jagger

by mediastinitis, pneumonia empyema or perforation into trachea or bronchi In 26 of the cases reviewed by Hedblom hair had been coughed up. Pressure on the heart or great vessels accounts for the early ages at which intra pericardial growths cause symptoms

(5) Pre sacral and coccygeal teratomas

(a) T₃pe

Most of these tumours are benign and cystic, and many of them contain highly organized structures such as loops of bowel digits or other parts of limbs (see below). Some of them however, are, or become malignant this usually appears to result from supervening adenocarcinoma, less often squamous cell carcinoma in one of the epithelial components of the growth rather than from malignancy in toto. Malignancy is seen even in infancy, as in the tumours with papillary adenocarcinoma described by Fletcher and Waring, Pandalai et al, Stewart et al and Lisco. or it may supervene in previously benign tumours of long duration in adults as in the cases of Pringle and Fuss.

(b) Site

Most of the tumours project promunently externally from the immediately pre sacral or pre coccygeal ussues they are often attached to the anterior surfaces of the lower sacral or ecocygeal vertebrae but in most cases these bones are intact. Only occasionally does the bulk of the tumour occupy the pelvis or project upwards into the abdomen, such tumours show that the retroperitoneal group and the sacrococcygeal group of teratomas differ only in level.

(c) Age

With rare exceptions sacroeoccygeal teratomas are already prominent, many of them bulky at birth. There is therefore no doubt that they arise at an early period of embryonic development.

(d) Sex

As with the retroperitoneal group there appears to be a decided preponderance of females (Hausmann and Berne Williams, 1935)

(6) Epignathi and teratomas of the skull base

Ahlfeld (1875) gave an excellent review of the earlier reports of epignathi, from which he concluded that 'Often neither the illustrations nor the reports enable us to decide whether the descriptions had a scientific basis or not. As to the contents of the tumours here also writers have often indulged in fantasy—comments still appropriate for many more recent descriptions.

(a) Type

Epignathi and basal cranial teratomas consist of well differentiated tissues often including highly organized structures, such as parts of limbs Malignant

the 25 cases with malignant tumours reviewed by Houghton was 27 Of the 5 intra pericardial tumours referred to in my 1946 paper, 3 were known to be congenital and 2 were found in subjects of 10 and 14 years. I have examined a benign cystic teritoma removed surgically from the anterior mediastrium of a man aged 67 whose only symptom had been aching pain in the chest for 4 months



Fig. 468—Intra pericardial teratoma from a male infant as seen after reflexion of parieta pericardium. T. - teratoma. H. - heart. A. - aorta. P. - pulmonary artery. L. lungs. (Billis 1946.). (Slightly reduced.)

(d) Sex

The sexes are nearly equally affected with perhaps a slight preponderance of females. Hedblom's review included 79 males and 92 females. Yet in striking contrast the malignant growths are almost restricted to males only 1 of the 25 cases reviewed by Houghton was a female.

(e) Secondary results

The main complications include mechanical effects on the tracheal great vessels heart or lungs infection and malienant change. Infection may be followed

(1) Component tissues

It is unnecessary here to describe the commoner tissues in detail, it must suffice to enumerate them briefly. They are adult or embryonic, mature or im mature. In beingn cystic teratomas the tissues are of mature adult type and are easy to recognize, but malignant growths contain embryonic tissues of all degrees of immaturity the recognition of which often demands much experience. This is especially the case when these and well differentiated tissues are intermingled. Only those who are well acquainted with the histology of the embryo at different ages can hope to identify many of the components of the more malignant teratomas. It must be emphasized here that the tissues of malignant teratomas are



Fig 469 - Chated respiratory epithelium in a teratoma (fron haematorylin stain) (× 1000)

not merely anaplastic but truly embryonic, reproducing in structure and differ entiation the tissues of the embryo and foetus. The mixture of differentiating tissues of all ages is one of the most striking structural characters of the malignant teratomas.

Skin, including hairs sebaccous and sweat glands and rarely pigmented (Fischl) or exhibiting pigmented moles (Lubarsch), is a very common component. So are stratified epithelium of orophary ngeal type associated with lymphoid tissue and mucous and mixed glands and respiratory pseudo stratified citated epithelium (Fig 469). Teeth or masses of tooth formative tissue are frequent, usually solitary or few but sometimes numbering dozens or even hundreds. Intestinal epithelium and glands are often present gastric and pancreatic tissues are less frequent (Figs 470–471). Liver tissue has only occasionally been recorded (Corsy Nicholson 1929 Fig 12). Lung tissue is very rare (Fig 472). Nondescript glands of various kinds are found most of these are probably related to alimentary or respiratory structures. The identification of adipose skin covered eminences as 'mammary glands' by Bland Sutton was fanoful.

members of the group have not been described, but the bearers of these growths seldom survive beyond the neo natal period

(b) Site

The epignathi are attached to the roof of the pharynx or palate from which they project into the mouth or nasal cavities. The base of the skull is not always affected, but in some cases the tumours have been hour glass shaped with intra cranial and extra cranial parts connected by an isthmus traversing the sphenoid as in the cases of Arnold and Kraus. It is clear that basal cranial and intracranial teratomas and epignathi differ only in the directions in which they tend to protrude as they grow. They all arise in the vicinity of Rathke's pouch the oral membrane and the anterior end of the notochord.

(c) Age

With rare exceptions the tumours have been fatal in the foctus or new born infant. Their time of origin is clearly during early embryogenesis

(7) Intracranial and intrathecal teratomas

Intracranial teratomas other than those arising from the base of the skull have been described and reviewed by Saxer, Askanazy, Barron, Hosoi, Harding and Naish McLean Bochner and Searff Denes and Russell I have studied the following two examples

Case II—Male aged 10 IIston—Headache vomiting and drowsiness for 7 weeks child previously normal and intelligent. Examination showed papilloedema and intelligent Examination showed papilloedema and intelligent Examination showed papilloedema papilloedema paper papilloedema paper papilloedema paper paper of left pulvinar and filled and distended posterior half of third ventricle aqueduct and upper half of fourth centricle. Tumour extended into left choroidal fissure and projected slightly into lateral ventricle and there was a separate small area of growth on ventricular lining I continue from the main mass. Cerebellium compressed but not invaded. Microscopical examination showed a disorderly mixture of the following tissues all immature and embryonic—squamous stratified epithelium much undifferentiated epitheliat tissue partly in the form of irregular networks and partly as diffuse or indefinitely elumped masses interspersed by collections of lymphocytes and therefore resembling seminoma in structure much undifferentiated mesenchyme and occasional islands of Joung cartilige.

Care III—(Binelly recorded in 1944 by Dr. R. Webster of Melbourne, who gave me one half of the specimen.) Necropsy on a female infant 9 weeks old with congenital hydrocephalus revealed a partly solid partly cybic teratoma. 14 centimetres in main diameter which appeared to have anisen from the region of the basal gangha and midhrain and which occupied the third and literal ventries and distended the crerbral cortex to a thin shell around it. the pineat corpus callosum and anterior commissure could not be identified the pions and cerebellium were intact. Microscopical examination revealed a great variety of young tissues including much central nervous tissue choroid pletus, pigmented neuro-epithelium respiratory squamous stratified and columnar celled epithelia various glandular structures renal tissue shin immature teeth bone carillage adipose tissue smooth and strated muscle filters. These were partly well different ated and partly embryonic and of different degrees of immaturity. Immature tissues predominated and musch undifferentiated cellular epithelium and mesenchyme were also present.

cerebrospinal fluid, and (c) in malignant growths, embry onic neuro epithelial tissue forming tubules layers lining cavities, or irregular networks (Fig. 473) and often

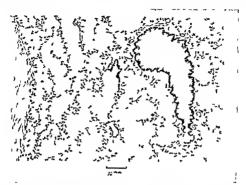


Fig. 472—Lung tissue in a teratoma of the brain from a female infant (Drawing b) G B Nicholson from specimen reported by Harding and Aush 1935) (×80)

mistaken for glandular structures. Peripheral nervous tissue occurs as nerve gangha of sympathetic type (see Fig. 493), nerve bundles usually accompanied by plentiful Schwann cells, and usually non medullated but sometimes medullated,

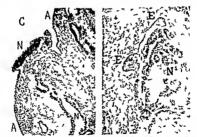


Fig. 473—Embryonic neuro-epithelial plaques and tubules (N) in continuity with a simple epithelium (A) and with squamous stratified epithelium (E) in walls of small cavities (C) in a testitudar teratoma (No. 1 Willis 1935 and 1936) (× 45)

and occasional well differentiated Paciman corpuscles (Kaboth, Hausmann and Berne Nicholson 1937 Fig 161, Willis, 1936, Masten) Ocular tissue is

Nerious tissue is present in at least four fifths of all teratomas (Willis, 1936).

Central nervous tissue occurs in benign growths as (a) masses of neuroghal tissue with characteristic staining properties usually astrocytic but sometimes containing



Fig. 470 - Gastric mucosa from teratoma shown in Fig. 468 (× 120)

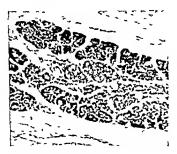


Fig. 47t —Pancreatic tissue with islets of Langerhans from teratoma shown in Fig. 468 (× 1°0)

also oligodendrocytes (Willis Fig 6 Barnard Fig 7) usually devoid of but sometimes containing nerve cells and with or without ependima lined carities (b) small or large cavities lined by fringes of choroid plexus and containing . mass of immature renal tissue resembling that of a nephroblastoma (Fig 475)

The cerebral teratoma of Case III above also contained embryonic renal tissue

Gental tissues have rarely been found. Kaboth recorded the presence of uterine tissue with endometrium in an ovarian teratoma. I depicted (Fig. 35, 1935) endometrium like tissue in a mediastinal teratoma and True and Guibert saw what they believed to be endometrial tissue with menstrual changes in a teratoma of the testis. In none of these cases can the identity of the tissue be regarded as certain and True and Guibert's identification is particularly dubious. The umbilical cords and placentas which have been identified in teratomas are all imaginary.

Chorionic and chorion epitheliomatous.

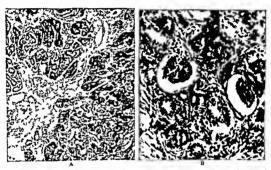


Fig. 475 — Embryome renal tissue in a solid retroperational teratoma from a female infant. A shows imperfect tubules and glomeruli and closely resembles nephroblastoma. B shows nearly fully formed glomeruli. (11-fills: 1935. Case X). (x: 50 and 100.)

tissue is almost certainly only a form of anaplastic epithelial growth associated with haemorrhage (see Chapter 33). The ovarian tissue seen by Gordon in a small mediastinal tumour may have been altered thyroid tissue. Testicular tissue has not been described except by Peyron who claimed to discover two nearly normal testes in a sacral teratoma from an infant 2 weeks old. Peyron is description and diagrammatic drawings are however very unconvincing, and his many groundless identifications of primitive anniotic vesicles. primitive streak allantors gonoblasts polyembryos and blastocysts in malignant testicular teratomas discredit the reliability of all his observations in this field.

Cartilage and bone in all stages of formation are very common. So also are adipose listue connective and vascular tissue, and in malignant growths undifferentiated embryonic mesenchime. Haemopoietic tissue is represented by bone marrow in masses of bone and by lymphoid tissue associated with orophary ngeal respiratory or intestinal epithelia.

sometimes represented by cavities lined by folded layers of deeply pigmented epithelium resembling that of the citiary body or by pigmented embryonic neuro-epithelium resembling that of the developing optic cup (Katsurada Abadic Corsy et al., Heijl, Kraus Dénes, and Fig 474), but no developed retina proper has been described and there is no justification for speaking of 'eyes in teratomas

The roll issue is not unusual, and it may be the bulkiest part of the growth Nicholson (1937) reviewed the subject of "ovarian goitres" and rightly warned against assuming these all to be teratomatous without proof yet of 67 cases, teratomatous tissues were demonstrated in the same ovary in no fewer than 23 Neumann (1937) saw 8 examples of thyroid ussue in the ovary in 5 of these the tumours were obvious teratomas, in 2 others teratomatous tissues were found

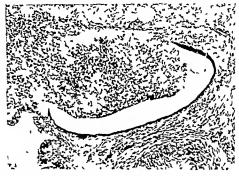


Fig. 474—Case III Small cavity in cerebral teratoma fined parily by embryonic nervous tistue and parily by deeply pigmented ocular epithelium (× 120)

only after painstaking search of exial sections and of the remaining specimen, in which only thyroid tissue was found only part of the timour was available for examination. It seems safe to conclude that most specimens of ovarian thyroid tissue are certifully teratomatous and that this is probably true of all in Emee's first case thyrotoxic symptoms abuted after removal of a thyroid continuing ovarian teratoma. In his second case one of seemingly pure ovarian gotter thyrotoxic symptoms developed along with recurrent peritonical metastrises of thyroid tissue and abated after removal of the metastasis laden omentum. Emge reviewed 9 reported cases of ovarian gottre with metastrises. Thyroid tissue has only occasionally been seen in teratomas other than ovarian e.g. in the pineal terrtomy, described by Bochner and Skarff.

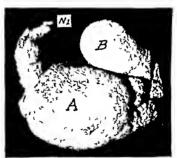
Reral tissue has only rarely been seen in teritomas (Budde Nicholson 1934 Willis 1935 Cases \ and \li\l\ My Case \ was remarkable in containing a

organogenesis. Such tissue correlations attain their greatest complexity in those teratomas which contain highly organized parts, now to be described

(3) Highly organized parts in teratomas

The most highly organized structures seen in teratomas include digits and other parts of limbs, pieces of intestine, pieces of cerebellium or cerebrum, sympathetic nerve ganglia and nerves, as well as those familiar components skin and teeth

Digits and Limbs 'Limbs have often been reported in teratomas when only digit bearing projections have been present Nicholson (1935 and 1937) and Gale and Willis (1944) described carefully examined specimens of digit bearing teratomas, and reviewed many previous reports Nicholson's 1937 paper contains the most complete description yet published of a tumour of this kind, his specimen was a sacrocoecygeal teratoma containing three unusually



Fio 477—Intracystic mass bearing a digit from retroperitoneal teratoma in a girl aged 13 A and B = two bulbous parts of mass which were attached to cyst wall by pedicle λ N1 = nait at end of digit (Gale and Wills 1944) (Natural size)

well formed digits with nails, phalanges and metacarpals

The specimen which Gale and I examined was from a retroperitoneal teratoma and included a single digit bearing two nails and containing easily recognizable but imperfect phalanges and a metacarpal (Figs. 477-479) Other records of well developed digits, hands or 'feet' in teratomas include those of Bohm. Budde, Seegers. Brines and Love and Mocrach. It is noteworthy that all of these concerned sacral or retroperitoneal tumours.

None of the 'limbs' described in teratomas deserves this title, digits are the most that have been demonstrated and although bars.

Intestine sometimes occurs in the form of eavities lined by perfect intestinal mucosa and with a two layered muscular coat including an Auerbach's piexus or in the form of even more fully developed clongated coils projecting into a

or masses of bone proximal to these have been called 'pelvis', radius', etc.,

these identifications are fanciful

Notochordal tissue has occasionally been reported, e.g. by Saver, Pandalai et al. and by Riopelle. However, notochordal tissue is not very distinctive histo logically and its identification in a teratoma must be very problematical. Pandalai et al. properly recognized this difficulty by speaking of 2 chordomatous? tissue in Riopelle's case the nature of the vacuolated tissue is very uncertain because of the admitted alteration of the tissues by faulty fixation and decalcification.

Smooth muscular tissue is very common around alimentary or respiratory eavities Striated muscle (Fig 476) is plentiful in some tumours and it is of interest that it may be abundant and well differentiated in a tumour in which peripheral nervous tissues are seanty or absent. This discrepancy raises the question whether teratomatous striated muscle can differentiate and maintain



Fig. 476 -Striated muscle fibres from same tumour as Fig. 475 (> 375)

its structure without any innervation. Studies of the innervation of muscle and other tissues in territomis are needed. Autsurada's is I believe the only report of earling muscle in a terratom.

(2) Tissue correlations in teratomas

At first plance the arrangement of the various tissues in teratomas, especially muligiant ones appears entirely haphazard and disorderly. Closer examination however soon discovers many chiracteristic associations of particular tissues resembling those of normal structures of the body (Nicholson Willis). Cavities lined by respiratory epithelium are often associated with cartilage cavities lined by intestinal epithelium are often associated with cartilage cavities lined by intestinal epithelium are often charicled by costs of smooth muscle masses of central network tissue are often surrounded by meninges like sheaths, and by masses of cartilage or hone teeth of course imply the orderly or relation of epithelial enamel and mesenchymal dentine and they are moteover often set in well developed bony sockets. These and other tissue relationships show the operation in the development of teratomatous tissues of dependent differentiation or the inductive effects of one growing tissue on another similar to those of normal

leptomeninges (Askanazy, Nicholson, 1929, Figs 8 and 9, Willis, 1935, Cases XI and XIII, and 1937, Cases XXIV and XXVIII) Well differentiated cerebellar cortex has been recorded by Askanazy, Landau, Willis (1939) and Bettinger

The degree of organization of peripheral nerves and ganglia in many teratomas is remarkable and raises interesting questions regarding the histogenesis and function of these structures. Thus nerves and nerve ganglia are often accompanied by abundant Schwann cells what is the origin of these? Well developed nerve ganglia, usually of distinctly sympathetic type, are often found far removed from central nervous tissue or even in tumours in which such tissue is scanty or appar ently absent, what is the origin of these ganglia? What tissues if any are innervated by the healthy looking nerves and ganglia which many teratomas contain and how are the developing nerves directed to their destinations? These questions must be answered by a closer study of the structure of teratomas of all ages and the answers will certainly be of interest to the student of the histogenesis of normal tissues. An interesting relationship was discovered by Nicholson in the digit containing teratoma described by him in 1937 the nerves which innervated the skin of the teratoma came from the sacral nerves of the The organism treats the tumour as flesh of its flesh by supplying it with sensory nerves and the skin of the tumour reacts as a physiological part by supplying the appropriate receptors An interesting research would be to examine a series of nerve containing teratomas by careful dissection or recon structions, with the object of distinguishing nerves supplied by the host from intrinsic teratomatous nerves

In considering highly organized structures in teratomas, it is well to recall that those very common components, skin and teeth are such structures Terato matous skin is often as perfect as normal skin, including well developed sebaceous and sweat glands hair follicles and arrector muscles Teeth also erupted or unerupted with their enamel dentine pulp and paradental epithelial residues are far from simple structures their formation involves interactions of the epithelial and mesenchymal tissues no less complex than those involved in the formation of a bone containing nail bearing digit. If teratomatous teeth were as rare as teratomatous digits they would excite the same wonder and lead to the same fanciful identifications of far more than is really present Induced even to day there are pathologists who would agree with Williams (1934) th teeth in a teratoma are evidence not only of an embry ogenetic parasitic formatio ch but also of cephalic derivatives thereof-heterotopic teeth being residua of the dental arcades of the parasite Those who have read Nicholson's papers however and those who have examined a few teratomas properly, will on the contrary conclude that teeth do not presuppose a mouth or a digestive system nor digits a limb or trunk Every highly organised part seen in a teratoma teaches the same lesson namely that its appearance here does not depend on the presence of other parts to which in normal ontogeny, it is anatomically related This last principle cannot be too strongly insisted on, those who will not admit it will continue to 'identify all manner of things which are not present (Gale ' and Willis)

coelomic cavity and possessing a pentoneal surface and a mesentery (Bohm, Hosmer, Kaboth, Hausmann and Berne, Schottenfeld and Littauer Willis, 1935 Case X Nicholson 1935, Fig 138)

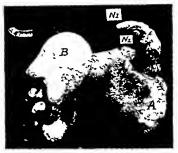
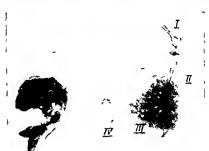


Fig. 478—Reverse aspect of mass in Fig. 477 showing projecting bone and teeth near pedicle and a second sub-terminal nail (N2) a large detached part of which is shown in inset. (Natura siz.)



I is 4°9—Skiagram of mass shown in I igs 477 and 478 showing digital bones I and II other nondescript bones III and IV and mass of bone and teeth near pedicle (Natural size)

Highly organi ed central nervous structures are frequent. Masses of brain like tissue often contain central cavities lined by ependyma and choroid plexus and filled with clear cerebrospinal fluid and are often surrounded by delicate

in this plastic ectoderm like tissue accounts for the continuity of young nervous tissue and epidermis which is often to be seen in teratomas (Figs. 480-484). In its later stages of differentiation teratomatous neural tissue resembles the spongio blastic mantle zone and the developing ependyma of the embryonic nervous system. As Nicholson observed, the development of choroid plexus in the walls



Fig. 482—From same tumour as Figs. 480 and 481, showing young nervous tissue (N) simple epithelium (E) and well formed young skin (S) in continuity with one another (× 45)

of neuro epithelial cavities is related to the close contiguity of ingrowing vascular mesenchyme. Pigmented optic neuro epithelium is always associated with and clearly derived from ordinary non pigmented embryonic neural tissue. The histogenesis of peripheral nerves and ganglia, commented on above needs investigation.

The histogenesis of teratomatous teeth is closely similar to that of normal teeth Tooth germs are developed in down growths of dental shelf tusue from cavities hined by octodermal epithelium mesenchymal dental papillae develop in relation



Fig. 483—Continuity of respiratory epithelium (R) squamous stratified epithelium (S) and well differentiated neurogial tissue (N) in an ovarian teratoma (Willie 1936 No X/V) (< 55)

to characteristic enamel organs with plentiful stellate reticulum, a bony alveolus often develops around the uncrupted tooth, and paradental residues of the dentifulation are to be found in the peridontal tissues within the alveolus (Fig 465, and see Willis 1935 Fig 27) Subsequent cruption of teeth into the epithelial cavities from which they originated ensues all the teeth in old beingn teratomas have crupted Defects in the enamel and dentine of old crupted teeth have been likened to caries, but the analogy is doubtful the defects are probably disintegrative changes comparable with the desquamation of epithelium and its

(4) The histogenesis of teratomatous tissues

Teratomus especially those containing a mixture of embryonic and maturing tissues, afford many opportunities for studying the genesis and differentiation of tissues in abnormal environments.

Small fragments of particular tissues are found growing in comparative isolation unassociated with structures to which they are



Fig. 480 — From a malignant teratoma of the ovary showing a cavity lined by simple epithelium (E) squamous statisfied epithelium (S) and young nervous tissue (N) continuous with one another (Wlln~1936~NeV)~(A-S)

related in normal ontogeny. The malignant embryonic teratoma is a great conglomeration of multiplying plastic constituents the differentiation of which though seemingly hapharard must be determined by local chemical conditions and tissue relationships as in normal embryogeness. What the teratomatous tissues can become in their scattered unanatomical positions is therefore of the greatest interest to students of normal histogeny.



Fig. 481—From same tumour as Fig. 480 showing a cavity lined by squamous stratified epithelium (SS) young nervous tissue (N) and choroid plexus (P) $(\times 65)$

advantage over the normal embryo for such studies that it often contains a great variety of tissues at all stages of maturity and in all possible situations with respect to one another

The histogenesis of teratomatous neural tissues was specially studied by the writer in 1936. It was shown that neuro opithelium takes origin from a simple plastic epithelium which like primitive embryonic ectoderm has also the potency of becoming epidermal or dental epithelium (Fig. 473). Divergent differentiation

showed stages in the differentiation of nodules of hyaline cartilage from mesen chyme especially in the neighbourhood of masses of developing central nervous tissue, the differentiation of zones of non strated muscle around developing epithelial cavities (Fig. 485), and the differentiation of strated muscle fibres in areas of undifferentiated spindle cells (Fig. 486). Lymphoid tissue develops chiefly in the walls of oropharyngeal respiratory or intestinal cavities. I have never seen either a well circumscribed lymph gland or splente tissue in a teratoma Haemopoiette bone marrow is found only within masses of bone.

(5) Variations of structure possibly related to situation

I have been struck by the abundance of central nervous tissue in intracrantal teratomas by the frequent presence of plentiful gastric and pancreatic tissue in thoracic and upper abdominal teratomas and by the fact that many of the teratomas containing digits or 'timbs' have been sacrecoccygeal or retropentoneal



Fig. 486—Thin strated muscle fibres revealed by iron haematoxylin stam in spindle celled tissue in a testicular teratoma. (Willis 1935 Case I) (× 500)

in position. Until a careful census is taken of all the tissues in a large series of teratomas it would be unsafe to generalize on this subject. but I think it probable that the nature and quantities of the tissues in teratomas may be in part related to the level of the body where the growths take origin. This proposition ments study.

MALIGNANCY AND METASTASIS OF TERATOMAS

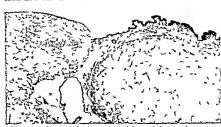
Malignancy in teratomas is of three distinct kinds (1) In a benign cystic teratoma a malignant tumour may arise from one of the previously quiescent tissues of the growth (2) in embryonic teratomas, like most of those of the testis malignancy is a property of the whole growth, shared by all its immature tissues, though not necessarily in equal degrees, and (3) rarely relatively benign ovarian teratomas produce implants of one or more tissues in the peritoneum

(1) Malignancy of a formerly benign cystic teratoma

This is most often squamous cell carcinoma arising from the skin of the growth as in cases reviewed and described by Stewart and Eglington Masson

replacement by phagocytic granulation tissue which is so frequent in senife teratomas

The lustogenesis of other epithelial tissues needs little comment. Skin, oro pharyngeal and respiratory epithelia are often associated and in continuity with



 F_{IG} 484 —Continuity of neuroglast tissue and glandular epithelium in the teratoma shown in F_{Ig} 466 $\,$ (\times 30)

one another in the walls of cavities, and they can clearly arise from a common precursor Salivary and other mixed glands develop as outgrowths from cavities limed by these epithelia Pancreatic tissue is always associated with intestinal cavities, and ducts may be seen entering these cavities (Willis 1935 Fig 19)

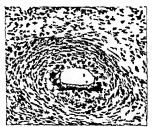


Fig. 485—Early differentiation of smooth muscle in mesenchyme around a young glandular structure in a teratoma of the testis (Willis 1935 Case III) (× 225)

Teratomas containing pancreatic tissue often contain gastric tissue also as in my intra pericardial specimen (Figs. 470, 471)

The lustogenests of mesenchymal tussues Embryonic teratomas often contain abundant undifferentiated mesenchyme and all stages can be traced in the development of muscle cartilage bone and connective tissue from this My 1935 paper

was at least 14 and prior to confluence of neighbouring tumours, had probably been 22. All of the reported tumours have been of benign type, composed of fully differentiated tissues including skin, teeth, respiratory and alimentary epithelia, central nervous tissue, nerves and ganglia (Fig. 493), cartilage, bone and adipose tissue.

In their benignancy the testicular teratomas of horses appear to contrast sharply with those of man, in whom malignant growths are the rule and benign ones the exception. It must be recalled, however, that the benign equine teratomas are found in coits corresponding in age to human children, and that most of the human testicular teratomas found during childhood are, like their equine counter parts, of benign type. Perhaps, then the seeming contrast between horse and man is largely accidental. Probably all human teratomas of the testis are present from early life in a benign form, and would be discovered unexpectedly at this stage if children were castrated as frequently as coits. Most human teratomas

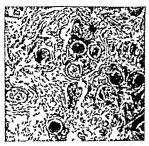


Fig. 493 —Well tormed sympathetic ganglion cells and nerve fibres in specimen shown in Fig. 492 (λ 72)

undergo malignant change in young adult life and become clinically evident only then perhaps some of the milignant testicular tumours seen in adult horses—which have often not been adequately studied or described—may be malignant teratomas similar to the human ones. More careful examination of the testes of gelded horses of various ages and of all equine testicular tumours along with more careful necropsy examination of young and old human testes may be expected to show the parallelism in the life histories of human and equine teratomas and to clear away some of the uncertainties regarding the genesis of these tumours.

(2) Gonadal teratomas in birds

Interest was focussed on avian teratomas by the Michalowsky (1926), later continuation (also copper s and Anissmowa) into the te development of la atom containing sk



l) and by g to Falin the rapid spiratory and Ochsenhirt, and Wilhs (1937) Rarely, carcinoma arises in some other epithelium, as in the cases of argentaffin carcinoma of ovarian teratomas described by Stewart, Willis and De Saram, and by Gabrilove and the cases of papillary



Fig. 487 —Case IV Squamous cell carcinoma of skin of ovarian teratoma (× 80)

adenocarcinoma of sacrococcygeal teratomas described by Fletcher and Wanng, Pringle, Pandalai et al. Stewart et al. and Lisco. The 5 specimens showing supervening malignancy which I have studied all ovarian were briefly as follows.

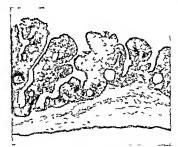


Fig. 488 -Case IV Pre invasive papillary carcinoma of teratomatous skin. (× 30)

Case IJ—(No VVI 1937) Woman aged 67 operative removal of ovarian cyst 20 centimetres in diameter containing hairs and sebum. Most of cyst wall was thin but in one place there was an eminence containing bone and 2 teeth and in another a projecting nodular mass of white growth 3 centimetres thick. Microscopically this was squamous-cell carunoma (Fig. 487). Other parts of the cyst epithelium showed thickening papillary overgrowth and many muloses (Fig. 488) and was clearly cancerous but in the

(a) voices the formerly most popular, and still quite prevalent, view as to the nature of teratomas, often expressed in the term 'embryoma'', (b) epitomizes the findings of the pathologist who has done more than any other to depreciate fantasy in the description of teratomas and to plead for 'uncoloured descriptions of specimens' and (c) is the conclusion of an experimental biologist who has realized that the careful objective study of teratomas holds much of interest for embryologists, and who incidentally, speaks of view (a) as 'this basic miscon cention.

It would be of little value to repeat in detail here the many and various hypotheses which have been advanced regarding the nature of teratomas—that they represented included twins (foetus in foetu) that they arose from fertilized polar bodies, or from dislocated blastomeres that they resulted from ovarian pregnancies, or from parthenogenic (or ephebogenic) proliferation of the germ cells of the bearer or even that testicular teratomas arose from isolated ovarian cells fertilized in the testis (Langerhans, cited by Cawadias). Those interested in these earlier speculations will find them outlined and criticized in Askanazy's excellent review and in Nicholson's writings. It will however be of interest to mention doubts which were voiced even during the last century.

(1) Early doubts regarding popular hypotheses

Peaslee's book on ovarian tumours (1873) contained a pertinent discussion of the ovarian pregnancy and foetus in foetu hypotheses both of which he rejected. From the diversity and maturity of their tissues, he concluded that all dermoid cysts are congential and that their origin must be referred to a very early period of embryonic life but he wisely abstained from formulating any definite hypothesis as to the nature of this early disturbance, saying, we must wait for the embryologist to answer these questions

The following remarks of Doran (1884) also are worth eiting pertinent question of the cause of the formation of these tumours in the ovary is a very profound one. Arguments must be founded on data, and I cannot see thit we are in any way sure of our data in this case. In science we must seek how processes begin we cannot always hope to find out why they begin. To talk of parthenogenesis or of foetal inclusion is in reality, not giving an explanation. To explain the growth of hair, bone teeth and glands in the ovary of an unimpregnated subject by saying that it is due to parthenogenesis is unscientific. It is more profitable to continue the examination of the tissues included within dermoid cysts than to indulge in speculations as to the origin of tumours of this class.

(2) The non foetiformity of teratomas

The hypotheses of twin inclusion parthenogenesis or ephebogenesis have this in common that they postulate that a teratoma is essentially a foctus—a vertebrate organism. Consequently those who adopted these hypotheses strove to see signs of foctiformity in every teratomal and the literature of the subject teems with spurious identifications of structures which they believed they saw if four expectation of sceing a thing is lively enough we will assuredly see it. (Nicholson 1934). Careful objective study of the structure of teratomas however shows

and alimentary epithelia, nervous ussues, cartilage bone striated muscle, etc. The results showed a striking seasonal difference most of the positive results being obtained (in the Northern hemisphere) when the birds were treated during the first 3 months of the year, i.e when spermatogenesis was most active. Bagg however, found that by the administration of pituitary gonadotrophic hormones successful results might be obtained as late as August.

What significance are we to attach to this peculiar result? In the first place it is to be noted that spontaneously occurring abdominal teratomas are not unusual in fowls, Mashar (1932) collected records of 13 examples But in view of the numbers of tumours recorded by the Russian workers and by Bagg (about 30 in all) and the restriction of these to the treated testes, the view that these were fortuitously discovered spontaneous growths is untenable. So also Kahlau's negative results in a small series of fowls is of little significance, though his finding that evsts lined by squamous or mucous epithelium may result from metaplastic changes in the gonadal tissues at the site of injection is a reminder that such structures alone do not constitute teratomas. However, the tumours described by Falm and co workers contained young neural tissue, choroid plexus striated muscle, and other components not to be explained by simple local meta plasia. It seems clear, then, that genuine teratomas have been produced in birds testes by the introduction of zine or copper salts. What relevance has this result for mammalian pathology? Does it disprove the origin of mammalian teratomas during embryonic life? I think not On other grounds already discussed the early embryonic origin of mammalian teratomas seems so undeniable that we must not attach too great a significance to results in creatures of an entirely different class. Let us recall that the experimental teratomas of fowls are not the only avian tumours the analogy of which with human tumours is doubtful there are also the filterable tumours and leucoses of birds which as was pointed out in Chapter 4, may not be comparable with mammalian tumours but may be peculiarly avian diseases. However this may be the experimental production of testicular teratomas in birds is a remarkable discovery and much more investigation of these tumours and their histogenesis is called for. There is need also of further attempts to produce tumours of mammalian gonads by the introduction of zinc salts or other substances (see Willis 1934)

THE NATURE AND HISTOGENESIS OF TERATOMAS

- (a) "A teratoma is an irregular conglomerate mass containing tissues and fragments of visecra belonging to a suppressed focus attached to an otherwise normal individual (Bland Sutton 1922)
- (b) A foetus without human form a body without regions organs without system shapes and proportions impossible absence of some unnatural multiplication of others—in short a light because it does not shine (Nicholson 1934)
- (c) 'What lies behind all the strange phenomena which we see in the teratomata is the failure of the individuation field at some point early in development to control the action of evocating substances (Needham 1942)

differentiate with a promiseuity and apparent haphazardness which precludes any possibility of their derivation from definitive germ layers, and to designate particular components is ectodermal entodermal or mesodermal while perhaps convenient descriptively, has no developmental meaning in these tumours. More over, they often show unomalous absence of a particular tissue, such as skin or nervous tissue or anomalous multiplieity of particular structures, such as hundreds of teeth, hundreds of separate little prieches of nervous tissue, hundreds of intestinal or respiratory cysts—characters not exhibited by the most degraded amorphous foetuses.

(3) Teratomas the result of disturbed embryonic chemistry

Askmazy (1907) was the first I believe to draw attention to the significance of Spemann's discoveries for the study of teratomas. From his eareful review of the structure and behaviour of these growths. Askanazy concluded that they must arise from abnormal tissue primordia in early embryonic life, the primordium might develop synchronously with the host to form a benign cystic teratoma, a teratoma adultum or coactaneum, or the primordium might remain quiescent for years and then proliferate as a malignant embryonic teratoma. What, he asked is the nature of this primordium? Is it a complex of different kinds of cells from all three germ layers or a self differentiating germ with potencies equivalent to those of an oxim? The second alternative must be the correct one. For Spemann had shown that organ rudiments are determined very early in embryonic life, and just as an optic cup has been shown to induce the formation of a lens in any region so it may well be that in the self-differentiation of ovi-equivalent teratoma germs similar inductive effects play an important part. Askanazy had thus attained to surprisingly modern concepts.

Not until two decades later did pathologists again turn to experimental embryology for light on the genesis of teratomas. In 1926, Budde discussed Spemann's work on the primary organizer and interpreted teratomas as the result of disturbances of the primitive streak. He drew attention especially to the situations of teratomas in median or paramedian positions from the base of the skull to the coccyx a distribution strongly supporting the concept of anom-

alies of the primitive streak and its derivatives

Like Nicholson and Needhum I am convinced that Askanazy and Budde were right in seeking the clue to the nature of teratomas in the study of organizers or morphogenetic ehemical substances of early embryonic development. The development of organizers in teratomas implies the interplay or mutual influence of neighbouring tissues on one another during their differentiation—influences of the nature of the embryologists second grade and third grade organizers (see Needham, 1942 p. 290 et seq.) But however perfect the local products of such influences may be, the teratoma lacks all signs of the operation of a primary or first grade organizer that presiding and dominant organizer which initiates axiation and orderly somatic development and determines that a mass of plastic living stuff shall become a vertebrate organism. As Nicholson said (1935) "what I miss in the established teratoma is the co-ordinating action of a whole upon its parts. In more scientific language evidence for the action it any stage of development of a dominant organizer for a body. Needham's

clearly the non foctiformity of these tumours. While it is true that some of the most reduced acardiac or amorphous foctuses lack demonstrable axial skeletons or regional parts as in Brodsry's specimen careful dissection or radiographic study reveals that most of them possess vertebrae and other regional bones or organs as in specimens described by Dictrich, Stewart (1914). Grogler (specimen No. 5), and van Tongeren (1932). This does not apply to teratomas not a single specimen of teratoma with an indubitable spine or with a plainty somatic distribution of parts has been described. Nicholson's detailed and critical examination (1934 and 1935) of supposedly foetiform teratomas (including the often cited specimens of Key, Repin, Shattock, Askanazy Ingier Heijl, Kaboth and Meyer) led him to conclude "that we do not accept foetiformity in a single object. Any unbiased reader of Nicholson's stimulating and amusing review will endorse this conclusion.

A point worth stressing here is that incomplete examination of a teratoma can give it of false resemblance to a focus. Thus in No XIII of my 1935 paper a single plane section of the growth (Fig. 28) could feasibly have been construed as showing a 'back' brain, "spinal cord' a suries of vertebrae, and an 'alimentary system. But complete examination shattered the illusion ind showed that the seemingly anatomical distribution of parts in the one plane was accidental

Here we must deal with the supposed 'vertebral column in an ovarian teratoma described in 1940 by Riopelle. This vertebral column, was a cylinder 15 millimetres long consisting in the mid line' entirely of cartilage but con taining on either side 3 ossified centres unequal in size and not symmetrically situated Laterally the 'vertebral bodies' gave off flat bony projections which curved backwards as neural arches partly fused into a single mass and devoid of articulations. The vertebral canal' contained a mass of central nervous tissue which was flanked by a series of ganglia from which issued nerves passing through 'invertebral foramina in the investing bone. Those familiar with the development of the spine will find it difficult to descry that structure in a continuous cartilaginous rod with irregular bony areas and projections even if these skeletal tissues partially enclose some nervous tissue and ganglia and even if some patches of vacuolated cells thought to be notochord are found in the right half of the rudimentary spine. Nor is our confidence in Riopelle's identification enhanced by seeing (in his Fig. 2) that the spinal cord and brain were separated by a septum of connective tissue by observing that the spinal ganglia were nearly as large as the vertebral bodies by reading of the plane of symmetry in what was clearly an asymmetrical structure Riopelle's vertebral column is in fact no more than an clongated partly cartilagmous partly bony mass encasing some nervous tissue-a well known relationship particularly commented on and depicted in my papers in 1935 and 1937

Not only do teratomas lack the essential part of a vertebrate organism a spinal axis but they possess no organs or true somatic regions. They contruin masses of central nervous tissue but no bruin respiratory or intestinal eysis or crinals but no respiratory or digestive systems renal tissue but no kidneys muscular tissue but no muscles. Teeth occur without a mouth tonsillar tissue without a pharynx and digits without a himb. In teratomas tissues and organisd structures 6000

and mediastinal tissues via the oral membrane. It is significant that most cervical teratomas affect the thyroid gland which is a derivative of an outgrowth from the oral entoderm close to the oral membrane.

(5) The primordial tissue of teratomas

Study of the structure of teratomas shows that active growth depends on the presence of immature tissues The most benign and quiescent teratomas consist of fully mature tissues with no signs of proliferative activity. The most malignant ones contain abundant immature embryonic tissues, some of them partially differ entiated some completely undifferentiated and resembling the tissues of very carly embryos All sorts of mixtures of mature and embryonic tissues are encountered in teratomas, and study of these mixtures makes it clear, as Jackson and Brues pointed out that while some of the multiplying tissues go on to maturity and become relatively quiescent, some of them continue to multiply as undifferentiated embryonic tissue. It is this undifferentiated pluripotent tissue which is the essential parenchyma of the tumour its differentiated tissues merely serve to show the range of its pluripotence Teratomas and the embryonic tumours of the nervous system kidney liver and other parts have this in common that they arise from and consist of embryonic tissue which continues to multiply at the embryonic level They differ in that while the embryonic tumours of particular organs have the stamp of regional determination upon them (though they show some latitude of differentiation not evinced by the normal parts) the teratomas are devoid or nearly devoid of regional determination. A teratoma is an embryonic tumour of pluripotential regionally non specific tissue, it is from such tissue that it must originally have arisen and it is such tissue that save for maturational changes. it continues to consist of and to produce. This concept of teratomas does not conflict with their frequently complete maturation to form benign quiescent lesions, for so also do embryonic neuroblastomas sometimes undergo complete maturation to form relatively quiescent benign ganglion uromas

The undifferentiated epithelial component of testicular teratomas (Figs 275 and 276 Chapter 33) may actually be the primordial tissue of these growths or sometiming not far removed from it. Its relationships show that it is a highly plastic tissue capable of divergent differentiation into neuro epithelium epidermis and glandular epithelia, and that it is also the tissue which when associated with haemorrhage or necrosis often assumes a chorion epithelioma like structure I am still uncertain as to its capacity to produce mesenchymal tissues though I have seen appearances which suggest this. If such a capacity were certainly established then this tissue would indeed have all the potencies essential to our hypothetical teratomatous primordium and to the undifferentiated tumour

parenchyma descended from it

(6) Conclusion

The age incidence, site incidence, structure, mode of growth and differentiation of teratomas along with a knowledge of recent advances in experimental embry ology all support the concept of teratomas developed in the preceding paragraphs. This is that teratomas are tumours arising from foci of plastic plumpotential embryonic tissue which escaped from the influence of the primary organizer during

identical conclusion has already been quoted at the beginning of this section Krafka (1936) attributed teratomas to aberrant activity of the primary organizer, which ' may eause the production of secondary embryonic axes in the primitive shield and lead to the formation of a teratoma at any site. This view essentially the same as Budde s must be rejected for the action of a primary organizer is as has just been insisted, the very thing that teratomas so plainly lack. These growths must arise from tissue foet which in early embryonic life suffered some kind of physiological isolation from the influence of the primary organizer, so that they failed to participate in the normal architecture of the body and underwent instead differentiation along divergent lines determined by purely local factors Experiments by Durken Vogt, Kusche and Holtfreter well summarized by Huxley and De Beer and by Needham have shown that isolated parts of the morula or blastula, removed from the influence of the primary organizer, undergo chaotic differentiation into a variety of tissues in accordance with their own "labile Teratomas show every sign of similar chaotic differentiation strongly suggesting that their embryonic primordia escaped early from all external influences and proceeded to differentiate in accordance with their own intrinsic labile determinations. The nature and cause of this escape are as yet unknown but increasing knowledge of the chemistry of the embryo will shed light on it Along with this elucidation there may well come also an explanation of the neoplastic quality of teratomas, which no doubt is intimately linked with the very chemical disturbance responsible for their genesis. The study of teratomas is thus of double interest, on the one hand to the embryologist because it concerns problems of early organogenesis and histogenesis on the other hand to the student of tumour causation because the very nature of neoplasia may first be revealed by closer study of these growths and of the disturbances of sterol chem istry which determine their formation

(4) The situations of teratomas

The situations of teratomas to the significance of which Budde drew special attention call for further comment. With relatively few exceptions teratomas arise in tissues which developmentally occupy immediately pre axial median or nearly median positions this applies to the gonadal sacrococcygeal retro peritioneal and eranial teratomas. As Budde rightly held this distribution strongly suggests the operation of disturbances emanating from the embryonic primitive streak and its invaginated derivatives the notochord and adjacent structures.

The only main exceptions to the rule that teratomas arise from tissues closely related to these structures are the anterior mediastinal and excited teratomas which are separated from the dorsal axis by the thoracie and cervical viscera But are they really exceptions to the general rule? Consideration of the early development of the head and neck shows that they are not. In the early embry o when the oral membrane is still imperforate there is no neck and the rudiments of the heart and other thoracie organs are in close juxtaposition to the oral region. It is only later when the head extends and the neck forms that the thoracie contents recede from their original juxta-oral position. Chemical disturbances emanating from the anterior end of the notochord or adjacent tissues during early embryogenesis might readily be transmitted to the prospective anterior cervical.

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early embryonic development, this escape being in some way related to disturb ances emanating from the invaginated organizing tissues of the primitive streak and so affecting median or para median parts in close relationship to these tissues The affected primordium as it grows differentiates in accordance with its own intrinsic 'labile determinations', producing a variety of tissues foreign to the part in which it grows. If these tissues differentiate and mature as fast as they grow a benign cystic teratoma results. If the tissues fail to mature completely but retain their capacity for continued growth at the embryonic level a malignant embryonic teratoma results. In some teratomas, notably in the testis, this capacity may be retained for many years by a small dormant teratomatous focus, which later evinces active growth and appears clinically as a progressive tumour during young adult life Such dormancy, though of great interest and meriting the closest study, is not peculiar to teratomas other kinds of malignant tumours also may display prolonged dormancy in recurrence or metastasis

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of disseminated growths in remote organs but without a demonstrable primary tumour in the uterus or tubes, have often been recorded (Zagorjanski Kissel, Munzer, Busse Dunger Walthard, Polano Christeller and Oppenheimer, Lapointe et al. Brews Brown et al.) The interpretation of such eases is often uncertain. We must first exclude possibly spurious eases in which a haemorrhagic carcinoma or teratoma may have been mistaken for chorion epithelioma but a number of unquestionably genume chorion epitheliomas will remain. There are two alternative explanations of these—either the seemingly primary extra genital growth was really a metastasis of a uterine or tubal primary tumour which had



Fig. 494 -A mass of chorionic syncytium in a large vein in a tubal pregnancy (× 120)

disappeared, or it was a genuine primary tumour arising from deported chorionic elements. There is little doubt that both of these events do occur, but in many cases it is difficult to decide which of the alternative explanations is the correct one. It is well known that in both normal pregnancy and in cases of hydatidiform mole emboli of chorionic epithelium or even entire placental villi are transported by the blood stream and lodged in neighbouring pelive tissues and in the lungs (Pick Veit, Marchand Dunger, Stevens, Hugbes). It is quite probable that extra genital primary chorion-epithelioma may occasionally take origin from these transported elements. Relevant in this connection also is the unusual condition of beingin multiple implants of chorionic villi found by Lazarus and Schiffin in various parts of the pentioneal cavity.

(3) Hydatidiform mole

About 50 per cent of chorion epitheliomas are known to be preceded by hydatuliform moles 25 per cent by abortions, and 25 per cent by apparently normal pregnancies (Novak Brews) Since mild degrees of hydatuliform change often escape recognition (Hertig and Edmonds) it is probable that this

CHAPTER 62

CHORION EPITHELIOMA

CHORION EPITHELIOMA IS unique in being a tumour of one individual transferred to another—a foetal tumour affecting the mother—Discussion of its instogeness is unnecessary, there is now universal recognition of its origin from the chorionic epithelium, and of the erroneousness of the old name—deciduoma malignum. It is a rare tumour—but it is impossible to assess its frequency accurately, because of the difficulty of distinguishing between invasive moles with atypical tissue and genuine chorion epitheliomas.

AGE INCIDENCE SITE AND CAUSATION

(I) Age incidence

As might be expected most chorionic tumours appear in women of child bearing age usually between 25 and 45 years. The interval elapsing between termination of the offending gestation and development of the tumour is usually only a few weeks or months, occasionally 2 or 3 years (as in Dunger's case) and tarely longer (e.g. apparently 8 years in the case reported by Brown et al.) As Novak pointed out, in cases with these long latent periods, the possibility of there having been an unsuspected intervening conception can rarely be excluded Post menopausal chorion epithelioma is very rare

- (2) Site
- (a) Primary uterine chorion epithelioma

The uterus is the primary site of the disease in at least 90 per cent of eases. In the uterus the growth arises from retained placental tissue following either normal pregnancy and delivery or abortion, with or without hydatidiform mole. There is good evidence that a primary uterine growth may sometimes be so small as to be removed by simple curettage, yet may have produced metastases (Novak and Koff), and such eases are difficult to distinguish from those in which the primary growth arises not from residual chorionic tissue in the uterus, but from tissue already deported to other situations (see below).

(b) Primary tubal or ovarian chorion epithelionia

Many instances of chorion epithelioma of a tubal gestation have been reported (Risel 1905 Thomas , Williams and other references by Lazarus and Schiftin) Supposed cases of primary ovarini chorion epitheliomi are difficult to interpret Risel (1914) described a case of disseminated chorion epithelioma of seemingly ovarian origin but the uterus showed a pigmented area which Risel regarded as evidence of a former uterine growth which had been expelled and this possibility remains also with other reported cases

(c) Primary chorion epithelioma in other sites

Cases of chorion-epithelioma of the vagina vulva or other pelvie organs, or

which this mistake has been made will, of course, show a high proportion of moles giving rise to 'chorion epithelioma" Estimates vary between 1 per cent and 40

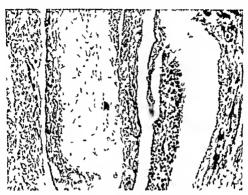


Fig. 497—Invasive hydatidiform mole—a large villus accompanied by much chorionic epithelium within a vein in the myometrium (× 100)



Fig. 498—Invasive hydatidiform mole a mass of chorionic epithelium in a large vein in the outer myometrium (× 120)

change precedes chorion epithelioma in the great majority of cases. The proportion of cases of hydatidiform mole to become chorion epitheliomatous is difficult to

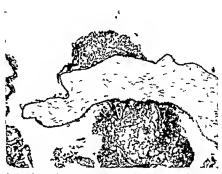


Fig. 495 —Hydatidiform mole – a large oedernatous villus with misses of overgrown charion epithelium (\times 40)

assess, partly because the milder degrees of the change escape diagnosis and partly because invasive moles have often been mistaken for chorion epitheliomas. Series in



Fig 496 -Detail of Fig 495 (x 120)

hydatidiform mole, in animals Ratcliffe reported having seen a rodent, Erithezon dorsatum, and Schlotthauer a dog, with chorion epithelioma, but without giving adequate details

STRUCTURE OF CHORION EPITHELIOMA

The grossly haemorrhagic and neurotic characters of this tumour are well known. Microscopically (Figs. 499, 500) areas of well preserved tumour tissue consist of irregular masses of polyhedral cells and fused syncytial masses. These are sometimes distinctive enough to be reminiscent of the hyperplastic chorionic epithelium of retained or hydatidiform placenta, but in many of the tumours the tissue is anaplastic and shows no real resemblance to its normal prototype. Invasion of blood-vessuls and mingled tumour and haemorrhage are pronunent features.

While the identity of a uterine tumour of this kind is clear enough, mistaken diagnoses of chorion epithelioma" have often been made with other tumours merely because they have been hacmorrhagic and have shown anaplastic growth



Fig 500 -Detail of Fig 499 (x 150)

with springita. It is to be insisted that the structure of chorion epithelioma is often not diagnostically distinctive and that it can be minucked by anaplastic caremoma, e.g. of the stomach or liver, and anaplastic teratoma of the testis or other parts (a v)

METASTASIS

The proclivity of chorion epithelioma to invade veins (see Schlagenhaufer, Schmauch Teacher, Cary) evplains the predominance of blood borne metastases in this disease. Lymph nodal metastases also occur, but are relatively infrequent and of fittle clinical importance

per cent or more, I agree with Novak that the lower figures are nearer the truth

Normal chorionic tissue can often be found invading veins in the wall of the uterus or tube and invasive mole may extend widely in this way and may show great syncytial overgrowth yet may be clinically being (Figs. 494-498). Invasion of veins does not per se denote malignancy which can be diagnosed confidently only when destructive extravascular extension is present. Microscopical distinction between atypical invasive mole and early chorion-epithelioma is difficult and not always possible. It is probable that being hydatidform mole, invasive mole (chorio-adenoma destruens.) and chorion-epithelioma form a continuous series with all transitions between them.

The structure and genesis of hydatidiform mole were carefully studied by Hertig and Edmonds who concluded that in most cases this disease is probably the result of early failure or defective development of the embryo so that no foetal

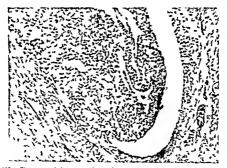


Fig. 499 —Chorion-epithelioma invading a large vein in the wall of the uterus (x 80)

circulation develops in the villi. Brews also pointed out that since fertility after a hydatidiform mole is often normal the factors responsible for the latter lie in the orum rather than in endocrine or other abnormalities of the mother. The nature of these factors is however still unknown.

(4) Chorion-epithelioma in animals

I have not encountered any clear reports of chorion-epithelioma or of

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(1) Regional venous embolic metastases

Blood borne metastases due to local retrograde embolism in the vulvo vaginal or other pelvic veins develop frequently. They appear as bluish or purple nodules in the vulva, vaginal walls bladder or broad ligaments and they are sometimes the first indications of disease (Munzer Teacher, Schmauch, my Case 219 recorded in 1934, and Brews s Case 11) These local venous metastases doubtless result from occlusion of large metrial and parametrial veins and consequent retrograde diversions of venous flow with tumour emboli into tributary vessels Metastases in the ovaries (Steinbaus, Risel 1914, Lufti and Schukru) are probably attributable to local venous embolism more often than to general dissemination

(2) Remote metastases

These occur first in the lungs often causing haemoptysis which is sometimes the first sign of the disease (Kelly and Teacher., Schiedemandel, Brown et al.) Dissemination beyond the lungs often produces metastases in many other viscera especially spleen intestines and brain. My 1934 review of 25 necropsy records in eases with blood borne metastases showed the lungs affected in 23 cases spleen in 15 intestine 15 brain 14 kidney 14 liver 13 pancreas 3, thyroid 2 stomach 2 heart 1, adrenals 1 and bone 1. In 9 eases in which the spleen or intestines contained metastases, the liver nevertheless escaped. Lufti and Schukru's base had metastases in the pituitary, thyroid adrenals gastric and duodenal mucosa, as well as more usual sites.

HORMONAL RESULTS

Both hydatidiform mole and chorion epithelioma are frequently accompanied by multiple luteal cysts of the ovaries and these are clearly the result of hormonal disturbances produced by the mole or tumour for they retrogress on removal of the latter. The strongly positive Aschheim Zondek test in cases of hydatidiform mole and chorion epithelioma is due to the secretion by these of gonadotrophic hormone similar to that of the normal placents. Rise or fall of the hormone titre in a case of mole or tumour under treatment is an important diagnostic and prognostic test (Roseler Gerritzen Cosgrove, Cuscaden and Bettinger) By follow up tests in a case of hydatidiform mole Cuscaden and Bettinger detected and successfully treated an early chorion epithelioma of the uterus. Extra uterine chorion epithelioma like extra uterine pregnancy produces decidual changes in the endometrium (Zagorjanski Kissel Busse Marchand, Christeller and Oucenheimer)

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